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METABOLISM
AND PRACTICAL MEDICINE

METABOLISM

AND

PRACTICAL MEDICINE

BY

CARL VON NOORDEN
PROFESSOR OF THE FIRST UNIVERSITY MEDICAL CLINIC, VIENNA

VOL. I.—THE PHYSIOLOGY OF METABOLISM

BY

ADOLF MAGNUS-LEVY
BERLIN

ANGLO-AMERICAN ISSUE UNDER THE EDITORSHIP OF
I. WALKER HALL
PROFESSOR OF PATHOLOGY, UNIVERSITY COLLEGE, BRISTOL; PATHOLOGIST TO THE BRISTOL ROYAL INFIRMARY

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PREFACE

An Anglo-American edition of von Noorden's well-known "Text-book of Metabolism" does not require any specific introduction.

Although the arrangement of the sections and their contents is the same as that of the first edition, the present text is mainly due to the co-operation of a number of workers in this branch of medical science. In his preface to the first German edition von Noorden acknowledged the encouragement and assistance of Gerhardt, von Jurgensen, and Riegel; in his introduction to the second edition he expresses his grateful thanks to the collaborators, "whose unflagging and zealous work alone has made it possible to bring out, instead of a second edition of my text-book, a handbook of the pathology of metabolism worthy of the extent and importance of the subject."

The additions made to the text have conformed to the general principle of the work in presenting a compilation of facts and a critical discussion of hypotheses, rather than the enunciation of theories. The bibliography has been also enlarged by the inclusion of recent English, American, and other papers. These addenda have been incorporated in the text. Any question of sponsorship may be easily settled by reference to the German copy.

It is a pleasure to express my thanks to my colleagues for their translations, to my friend Professor T. H. Milroy for many valuable suggestions, and to the University College Demonstrator in Pathology, Dr. Carey Coombs, for his careful preparation of the index.

I. WALKER HALL.

Bristol, 1907.

CROCKER

INTRODUCTION

In this Anglo-American edition I wish to add a few words to the preface written for the German original. I congratulate myself heartily that my publishers decided to issue an English translation of my text-book immediately after the German edition had appeared. It was a bold stroke on their part to do so before the commercial success of the German volume was definitely assured. Yet I believe that their courage will be rewarded, and for this reason: a few decades ago the scientific examination of the processes of metabolism was almost confined to investigators of the German, French, and Italian nations ; but in the last twenty years a number of English and American men of science have turned their attention to this branch of scientific medicine, and we have to thank their careful labours for a number of admirable publications that have added much to our knowledge. Among these I may mention the names of Halliburton, Hopkins, Vaughan Harley, Starling, Milroy, Leathes, and Walker Hall in England, and of Atwater, Benedict, Chittenden, Folin, Herter, Mendel, and G. Lusk in America. It is, indeed, my conviction that the rising generation of English and American medical men regards the problems of metabolism with an interest that grows from year to year, and that these men will eagerly welcome this book as a trustworthy guide and a stimulating source of information.

It gives me particular pleasure to state that my friend Professor I. Walker Hall has undertaken the laborious task of editing this edition of my work, published in Chicago by Messrs. W. T. Keener and Co., and in London by Mr. William Heinemann. No person better fitted for this difficult duty could have been found, as I knew when I commended him for the purpose to my publishers. I believe that my English-speaking colleagues will agree with me when I say that Professor Walker Hall has acquitted himself brilliantly, and I herewith convey to him my most heartfelt good wishes and thanks.

CARL VON NOORDEN,
Professor of the First University Medical Clinic.

Vienna,
February 3, 1907.

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LITERATURE

The following abbreviations are used throughout:

A. C.	Annali di Chimica.
A. c. p.	Annales de Chimie et de physique.
A. C.-Z.	Allgemeine medicinische Central-Zeitung.
A. D.	Arbeiten des pharmakologischen Inst. zu Dorpat.
A. D. S.	Annales de Dermatologie et de Syphilologie.
A. F.	Archivio di Farmacologia e Terapeutica.
A. F. s.	Archivio di Farmacologia sper.
A. H.	Archiv der Heilkunde.
A. i. B.	Archives italiennes de Biologie.
A. J. M. S.	American Journal of the Medical Sciences.
A. J. O.	American Journal of Obstetrics.
A. J. P.	American Journal of Physiology.
A. J. U.	American Journal of Urology.
A. K.	Arbeiten aus der städtischen Krankenh. zu Frankfurt-a-Main.
A. k. G.	Arbeiten aus dem kaiserl. Gesundheitsamte.
A. L. I.	Arbeiten aus dem Leipzig physiolog. Institut.
A. M.	Archives of Medicine (New York).
A. P.	Anat. physiol. Untersuchungen (Wien).
A. p. H.	Archiv für physiologische Heilkunde.
A. Ph.	Archivio di Pharmakoterap.
A. S. B. A. s. b.	Archives de Sciences biologiques, St. Petersb.
A. T. S.	Archiv für Tropen und Schiffshagg.
Ac. T.	Accademia medica di Torini.
An. c. F.	Annali di Chimica e di Farmacologia.
An. c. P.	Annalen der Chemie und Pharmacologie.
An. g.-u.	Annales des Maladies des organes génito-urinaires.
An. gy.	Annales de gynécologie.
An. hy.	Annales d'hygiène publique.
An. I.	Annali d'Igiene sperimentale.
An. m.-p.	Annales médico-psychologiques.
An. P.	Annales de l'Institut Pasteur.
An. S.	Annals of Surgery.
An. S. K.	Ann. Städt. Allg. Krankenh. (München).
An. T.	Annales de Thérap. dermat. et syphil.
An. u.	Annales univ. de Méd. et Chirurgie.
Ar. A. P.	Archiv für Anatomie und Physiologie.
Ar. B.	Boas's Archiv.
Ar. c. B.	Archives cliniques de Bordeaux.
Ar. D. S.	Archiv für Dermatologie und Syphil.
Ar. E. O.	Archiv für Entwickelungsmech. der Organismen.

Ar. F.	Archivio di Fisiologia.
Ar. g. m.	Archives générales de Médecine.
Ar. Gy.	Archiv für Gynäkologie.
Ar. H.	Archiv für Heilkunde.
Ar. h. B.	Archiv für die holländischen Beitr. z. Natur.- und Heilkunde.
Ar. Hy.	Archiv für Hygiene.
Ar. i. B.	Archives italiennes de Biologie.
Ar. i. M.	Archivio italiano di Clinica Medica.
Ar. i. P.	Archives internat. de Pharmac. et de Thérap.
Ar. K.	Archiv für Kinderheilkunde.
Ar. k. C.	Archiv für klinische Chirurgie (Langenbeck's).
Ar. M.	Archiv für klinische Medicin.
Ar. m. A.	Archiv für mikroscop. Anatomie.
Ar. m. ex.	Archives de médecine expérimentale.
Ar. n.	Archives de Névrologie.
Ar. p. A.	Archiv für patholog. Anat. und Physiol. (Virchow).
Ar. P.	Archives de Physiologie.
Ar. P. M.	Archiv für die gesammte Physiol. des Menschen (Pflüger's).
Ar. P. N.	Archiv für Psychiatrie und Nervenkrankh.
Ar. P. P.	Archiv für exper. Pathologie und Pharmakologie.
Ar. Ped.	Archives of Pediatrics.
Ar. Ph.	Archives of Physiology.
Ar. R. R.	Archives of the Roentgen Ray.
Ar. S.	Archives of Surgery.
Ar. S. M.	Archivio per le Scienze mediche.
Ar. s. p.	Archives des Sciences physiques et naturelles.
Ar. T.	Archiv für wissenschaftliche und prak. Tierheilk.
Ar. V.	Archiv für Verdauungskrankheiten.
Arb. M.	Arbeiten aus dem med.-klin. Inst. zu München.

B. A.	Berlin Akademy.
B. A. P.	Beiträge zur Anat. und Physiologie.
B. B.	Berichte der Bayer. Akad. der Wissen.
B. C.	Biologisches Centralblatt.
B. C. G.	Berichte aus der Chemische Gesell.
B. d.	Berichte der deutsche pharm. Gesell.
B. D. N.	Berichte der Dorpater Naturforsch. Gesell.
B. J.	Biochemical Journal.
B. J. C. D.	British Journal of Children's Diseases.
B. J. D.	British Journal of Dermatology.
B. K.	Berliner Klinik. Sammlung klin. Vorträge.
B. K. T.	Beiträge zur Klinik der Tuberkulose.
B. k. W.	Berliner klinische Wochenschrift.
B. M. J.	British Medical Journal.
B. M. R.	Birmingham Medical Review.
B. M. & S. J.	Boston Medical and Surgical Journal.
B. M. v.	Bulletin de la Soc. centr. de Méd. vét.
B. p. G.	Berlin phys. Gesellschaft.
B. roy. M.	Bulletin de l'Académie roy. de Médecine.
B S. A.	Berichte der Sächs' Akademy.
B. S. P.	Bulletins et Mémoires de la Soc. anat. de Paris.
Be. A. P.	Beiträge zur pathol. Anat. (Zeigler)

Be. C.	Beiträge zur klin. Chirurgie.
Be. P. P.	Beiträge zur chem. Physiol. und Pathol. (Hofmeister).
Bel. m.	Belge médical.
Bi. C.	Biochemisches Centralblatt.
Bib. M.	Bibliotheca medica.
Bio. C.	Biophysikalisches Centralblatt.
Bo. G.	Bollettino della r. Accad. med. di Genova.
Br. M.-C. J.	Bristol Medico-Chirurgical Journal.
Brain.	Brain.
Bu. g. t.	Bulletin général de Thérapeutique.
Bu. H.	Bulletins et Mémoires de la Soc. méd. d. Hôp. de Paris.
Bu. J. H. H.	Bulletin of Johns Hopkins Hospital.
Bu. L.	Bullettino della Soc. Lancisiana degli Ospedali di Roma.
Bu. M.	Bulletin médical, Le.
Bu. P.	Bulletin de l'Acad. de Médecine (Paris).
Bu. R.	Bullettino della Reale Accademia med. di Roma.

C. a. P.	Centralblatt für allgemeine Pathologie.
C. B.	Chemisches Berichte.
C. C.	Centralblatt für Chirurgie.
C. G.	Centralblatt für Gynäkologie.
C. H.	Centralblatt für Haut- und Geschlechtskr.
C. i. M.	Centralblatt für innere Medicin.
C. J.	Clinical Journal.
C. J. M.	Cleveland Journal of Medicine.
C. K.	Centralblatt für die Krankh. d. Harn- und Sex. Org.
C. k. m.	Centralblatt für klinische Medicin.
C. M.	Centralblatt für d. gesammte Medicin.
C. M. i.	Clinica medica italiana.
C. M. Pa.	Clinica medica gener. di Parma.
C. m. W.	Centralblatt für die medicinischen Wissenschaft.
C. N.	Centralblatt für Neurologie.
C. P.	Centralblatt für Physiologie.
C. r. A. M.	Compte-rendu de l'Acad. de Médecine.
C. r. A. S.	Comptes rendus de l'Académie des Sciences.
C. r. S. B.	Comptes rendus des Séances et Mém. de la Soc. de Biologie.
C. S.	Centralblatt für Stoffwechsel und Verdauungs-krankh.
C. s. A.	Correspondenz-Blatt für schweizer Aerzte.
C. St.	Clinical Studies (Bramwell).
C. Z.	Chemisches Zeitung.
Ch. An.	Charité Annalen.
Cl. M.	Clinica moderna, La.
Co. M.	Congrès français de Médecine.
Ct.B.	Centralblatt für Bakteriologie.
Ct. P. S.	Centralblatt für d. ges. Phys. u. Path. des Stoffwechsel.
Ct. T.	Centralblatt für gesammte Therapie.

D. A.	Dubois Archiv.
D. Ar. M.	Deutsches Archiv für klin. medicin.
D. J. M. S.	Dublin Journal of Medical Science.
D. K.	Deutsche Klinik.
D. m. W.	Deutsche medicinische Wochenschrift.
D. M.-Z.	Deutsche Medizinal-Zeitung.

D. Z.	Deutsche Aerzte-Zeitung.
D. Z. C.	Deutsche Ztschr. für Chirurgie.
D. Zt.	Dermatologisches Zeitschrift.
E. A.	Experimental Archiv.
E. H. R.	Edinburgh Hospital Reports.
E. M. J.	Edinburgh Medical Journal.
Eng. A.	Engelmann's Archiv.
Er. P.	Ergebnisse der Pathologie (Lubarsch u. Ostertag).
Er. Ph.	Ergebnisse der Physiologie (Ascher u. Spiro).
F. B.	Festschrift für Bischoff.
F. h.	Folia hæmatologia.
F. L.	Finska Läkarsällskapet's Handlingar.
F. M.	Fortschritte der Medicin.
F. P.	Florence Labor. de Physiol. Résumé des Travaux
G. m. B.	Greifswalder medicinische Beiträge.
G. M. C.	Mitteil. a. d. Grenzgebieten der Med. und Chir.
G. M. J.	Glasgow Medical Journal.
G. m. P.	Gazette médicale de Paris.
G. O.	Gazzetta degli Ospedali.
G. O. C.	Gazzetta Ospedali e Clin.
G. T.	Gazzetta medica di Torino.
Ga. H.	Gazette des Hôpitaux.
Gi. i. S.	Giornale internaz. d. Scienze med.
Gi. M. v.	Giornale ital. della Mal. ven. e della pelle.
Gi. T.	Giornale d. reale Accademia di Med. du Torino.
Gu. H.	Guy's Hospital Reports.
Gz. H.	Gazette hebdomadaire.
H.	Hospital.
H. C.	Hygienisches Centralblatt.
H. R.	Hygienisches Rundschau.
H. S. Hos.	Hospitalstidende.
I. D. C.	International Dermatological Congress.
I. M. C.	International Medical Congress.
I. R.	Internationale klinische Rundschau.
I. T. C.	International Tuberculosis Congress.
In. C.	International Clinics.
In. C. L.	Internat. Centralb. f. Laryngologie.
J. A. M. A.	Journal of the American Medical Association.
J. A. P.	Journal de l'Anatomie et de la Physiologie.
J. A. & P.	Journal of Anatomy and Physiology.
J. B. C.	Journal of Biological Chemistry.
J. B. & C.	Journal of Balneology and Climatology.
J. C.	Journal of the American Chemical Society.
J. C. D.	Journal of Cutaneous and Gen.-Urin. Diseases.
J. D. S.	Journal de Dermat. et de Syphil.
J. E. M.	Journal of Experimental Medicine.
J. H. H. R.	Johns Hopkins Hospital Reports.

J. Hy.	Journal of Hygiene.
J. La.	Journal of Laryngology, Rhinology, and Otology.
J. M.	Journal des Maladies Cutan. et Syph.
J. M. B.	Journal de Médecine de Bordeaux.
J. M. R.	Journal of Medical Research.
J. M. Sc.	Journal of Mental Science.
J. mil.	Journal de Médecine militaire.
J. N. & M.	Journal of Nervous and Mental Disease.
J. O. & G.	Journal of Obstetrics and Gynæcology of the British Empire.
J. P.	Journal of Physiology.
J. P. & B.	Journal of Pathology and Bacteriology.
J. P. C.	Journal für prakt. Chemie.
J. P. P. G.	Journal de Physiologie et de Pathologie générale.
Ja. G.	Jahrbücher über Gynäkol. und Geburtsch.
Ja. H.	Jahrbücher d. Hamburgischen Staatskrank.
Ja. K.	Jahrbücher für Kinderheilkunde.
Ja. M.	Jahrbücher der in- und auslandischen gesammte Med. (Schmidt).
Jan.	Janus.
Jb. L. M.	Jahresbericht ü. d. Leistungen u. Fortschr. in d. ges. Med.
Jb. L. O.	Jahresber. u. d. Leist. u. Fortschr. in Gebiete der Ophth.
Jb. T.-C.	Jahresber. u. d. Fortschr. der Thier-Chemie.
Jo. B.	Journal de Médecine (Bruxelles).
Jo. P.	Journal de Pharmacie et de Chimie.
K. i. M.	Kongress für innere Medicin.
K. J.	Klinisches Jahrbüch.
K. S.	Korrespondenz-Blatt für Schweizer Aerzte.
K. T. W.	Klinische-Therapeutische Wochenschrift.
K. V.	Korrespondenz-Blätter d. allg. ärztl. Vereins von Thüringen.
K. W.	Korrespondenzbl. d. Württemb. ärztl. Landesv.
L.	Lancet.
L. m.	Lyon médical.
La. R.	Laboratory Reports, Roy. Coll. Phys., Edinburgh.
Li. M.-C. J.	Liverpool Medico-Chirurgical Journal.
M.	Morgagni, Il.
M. A. B.	Mémoires de l'Acad. roy. de Belgique.
M.-C. T.	Medico-Chirurgical Transactions.
M.-C. U.	Medicin.-Chemische Untersuchungen.
M. Chr.	Medical Chronicle.
M. H.	Middlesex Hospital.
M. i.	Médecine infant., La.
M. K.	Medicinische Klinik.
M. M.	Medical Magazine.
M. m.	Médecine moderne, La.
M. M. J.	Montreal Medical Journal.
M. N.	Medical News.
M. N. A.	Memoirs of the National Academy of Sciences.
M. O. A.	Magyar Orvosi Archivum.
M. R.	Medical Record.
M. Rev.	Medical Review.
M. T.	Medical Times and Gazette.
Ma.	Maly's Jahrbuch.

Mit. B.	Mitteilungen aus der Berlin phys. Gesell.
Mit. H.	Mitteilungen aus der Hamburg. Staatskrankenanstalten.
Mit. K.	Mitteilungen aus der med. Klinik zu Königsberg.
Mit. U.	Mitteilungen der Kgl. Ges. d. Wiss. zu Upsala.
Mit. W.	Mitteilungen aus der med. Klinik zu Würzburg.
Mo. C.	Monatsschrift für Chemie.
Mo. D.	Monatshefte für praktische Dermatologie.
Mo. G. G.	Monatsschrift für Geburtsch. und Gynäkologie.
Mo. K.	Monatsschrift für Kinderheilkunde.
Mo. m.	Montpelier médical.
Mo. U.	Moleschotts Untersuch. zur Naturlehre.
Mü. m. W. Mu. m. W.	Münchener med. Wochenschr.
N. A. S.	Memoirs of the National Academy of Sciences.
N. B.	von Noorden's Beiträge.
N. C.	Neurologisches Centralblatt.
N. C. T.	Nuova clin. terap., La.
N. I. S.	Nouvelle Iconographie de la Salpêtrière.
N. k. A.	von Noorden's klinische Abhandlung.
N. m. A.	Nordiskt medicinskt Arkiv.
N. T.	Nederlandsch Tijdschrift voor Geneeskunde.
N. V.	Naturw. Verein. f. Neuvorpommern.
N. Y. J.	New York Medical Journal.
N. Y. M.	New Yorker medicinische Monatssch.
N. Y. & P. J.	New York and Philadelphia Medical Journal.
P.	Policlinico, Il.
P. L.	Przeglad Lekarski.
P. m.	Presse médicale, La.
P. m. b.	Presse médicale belge, La.
P. M. J.	Philadelphia Medical Journal.
P. P. C.	Proceedings of the Philadelphia County Medical Society.
P. R.	Proceedings of the Royal Society (London).
P. R. Ed.	Proceedings of the Royal Society of Edinburgh.
P. T.	Philosophical Transactions of the Royal Society.
P. V.	Prager Vierteljahrsschr.
P. W.	Prager medizinische Wochenschrift.
Pa. M. T.	Philadelphia Medical Times.
Ped.	Pediatria, La.
Pr.	Practitioner.
Pro. M.	Progressive Medicine.
Pro. mé.	Progrès médical, Le.
R. c.	Revista clinica.
R. c. c.	Rivista critica clinica.
R. c. M.	Rivista gén. ital. di clin. med.
R. c. P.	Rivista di clin. Pediatr.
R. c. t.	Revue générale de clinique et thérapeutique.
R. M.	Riforma medica.
R. M. E.	Revue mensuelle des Mal. des Enfance.
R. m. M. C.	Revue mensuelle de Méd. et Chir.
R. m. R.	Russische medicin. Rundschau.
R. N. P.	Review of Neurology and Psychiatry.

R. P.	Russische Arch. der Pathologie.
R. T.	Revue de Thérapeutique.
R. v.	Rivista veneta di Scienze mediche.
R. Z. D.	Russische Ztschr. f. Dermat.
Re. C.	Revue de Chirurgie.
Re. Gy.	Revue de Gynécologie et Chir. abdom.
Re. M. Re. m.	Revue de Médecine.
Ri. c.	Rivista clinica e terapeutica.
Riv. M.	Rivista di medicina.

S.	Sperimentale, Lo.
S. B.	Société de Biologie.
S. b. A.	Sitzungsber. d. königlich-bayer. Akad. d. Wiss. zu Münch.
S. E.	Sitzungsber. der physikal.-med. Soc. zu Erlangen.
S. J.	Scottish Medical and Surgical Journal.
S. K.	Sitzungsber. d. Kaiserl. Akad. d. Wissen. (Math.-natur. Kl.).
S. M.	Sitzungsber. d. Gesell. f. Morphol. u. Physiol. zu München.
S. m. A.	Sammlung med. Abhandlung.
S. m. H.	Société méd. d. Hôpitaux.
S. n. G.	Sitzungsber. d. niederrh. Gesell. f. Natur.- und Heilkunde.
S. W.	Sitzungsber. d. phys.-med. Gesell. zu Würzburg.
S. W. A.	Sitzungsber. d. Kaiserl. Akad. d. Wissen. (Math.-natur. Kl.).
S. W. D.	Sitzungsber. d. Wien dermat. Gesell.
Sc. W.	Schweiz Wchnschr. f. Chem. u. Pharm.
Se. M.	Semaine médicale.
Set. M.	Settimana medica, La.
Sit. M.	Sitzungsber. d. Gesell. z. Beforderung d. Ges. Nat. z. Marburg.
Sk. Ar. P.	Skandinavisches Archiv für Physiologie.
St. B. H.	St. Bartholomew's Hospital.
St. B. J.	St. Bartholomew's Hospital Journal.
St. P.	St. Petersburger medicin. Wochenschr.
St. T. H.	St. Thomas's Hospital.

T. A. A. P.	Transactions of the Association of American Physicians.
T. A. S. A.	Transactions of the American Surgical Association.
T. C. P. P.	Transactions of the College of Physicians of Philadelphia.
T. Cl. S.	Transactions of the Clinical Society of London.
T. Co. A. P.	Transactions of the Congress of American Physicians and Surgeons.
T. F.	Travaux du Laboratoire de L. Frédéricq.
T. G.	Therapie de Gegenwart.
T. M.	Therapeutische Monatsshefte.
T. M. S.	Transactions of the Medical Society of London.
T. O. S.	Transactions of the Obstetrical Society of London.
T. P. S.	Transactions of the Pathological Society of London.
Th. G.	Therapeutic Gazette.

U. A. M.	Ungarisches Archiv für Medizin.
U. m.	Union médical, L'.
U. M. M.	University Medical Magazine.
U. P.	Ungarische Medizin.-chir. Presse.
U. Pa.	University of Penna. Med. Bulletin.
U. S. D. B.	United States Department of Agriculture Bulletin.

V. b. A.	Verhandl. d. böhmischen Akad. der Wissensch.
V. B. M.	Verhandl. d. Berliner medicin. Gesell.
V. C. M.	Verhandl. d. Congresses f. inn. Med.
V. d. G.	Verdandl. d. deutschen pathol. Gesell.
V. f. A.	Verhandl. d. finnischen Aerzte.
V. G. K.	Verhandl. d. Gesell. f. Kinderh.
V. i. M.	Verein für innere medicin zu Berlin.
V. K. D.	Verhandl. d. Kongr. d. d. Dermat. Gesell.
V. n. A.	Verhandl. d. d. naturfors. u. Aerzte.
V. n. G.	Verhandl. d. naturforsch. Gesell. in Basel.
V. n. V.	Verhandl. d. Naturf.-Versamm. in Meran.
V. p. G.	Verhandl. d. physiol. Gesell. in Berlin.
V. s. G.	Verhandl. d. Schles. Gesell. f. vaterl. Kultur.
V. W. G.	Verhandl. d. phys.-med. Gesell. in Würzburg.
Vo. s. V.	Volkmann's Sammlung klin. Vorträge.

W.	Wratsch.
W. A.	Wiener Akademie.
W. Ab.	Würzburger Abhandl. a. d. Gesam. der prak. Heilk.
W. J.	Wiener medicinische Jahrbücher.
W. K.	Wiener Klinik: Vortr. a. d. gesamm. prak. Heilk.
W. k. R.	Wiener klinische Rundschau.
W. k. W.	Wiener klinische Wochenschrift.
W. L. J.	West London Medical Journal.
W. m. B.	Wiener medicinische Blätter.
W. m. P.	Wiener medicinische Presse.
W. m. W.	Wiener medicinische Wochenschrift.
W. V.	Würzburger Verhandlungen.
W. Z.	Wiener Zeitschrift.

Y. J.	Yates and Johnson Laboratory Reports.

Z. a. C.	Zeitschrift für anal. Chemie.
Z. a. P.	Zeitschr. f. allg. Physiologie.
Z. B.	Zeitschr. f. Biologie.
Z. C.	Zeitschr. f. angewandte Chemie.
Z. d. p. T.	Zeitschr. f. diätet. und physikal. Therapie.
Z. e. P.	Zeitschr. f. exper. Pathologie.
Z. G. G.	Zeitschr. f. Geburtsch. u. Gynäkol.
Z. H.	Zeitschr. f. Heilkunde.
Z. Hy.	Zeitschr. f. Hygiene.
Z. M.	Zeitschr. f. klin. Medicin.
Z. N.	Zeitschr. f. Nervenheilkunde.
Z. P.	Zeitschr. f. Psychologie.
Z. P. A.	Zeitschr. f. allg. Pathol. und path. Anat.
Z. p. A.	Zeitschr. f. prakt. Aerzte.
Z. P. C. Z. p. c.	Zeitschr. f. physiol. Chemie.
Z. r. M.	Zeitschr. f. rationelle Medizin.
Z. T.	Zeitschr. f. Tuberkulose.
Z. V.	Zeitschr. f. Vatermarkande.
Ze. P. P. S.	Zentralbl. f. d. gesamm. Physiol. und Path. d. Stoffwech.

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THE PHYSIOLOGY OF METABOLISM

BY ADOLF MAGNUS LEVY[1]

UNIV. OF

> "Eine einzige Zahl hat mehr wahren und bleibenden
> Wert als eine kostbare Bibliothek voll Hypothesen."
>
> ROBERT MAYER.

No branch of pathology is so capable of being expressed by actual figures—the results of experimental determinations—as that of metabolism. Although the time has not yet come for this branch to take the place and the significance of a precisely exact science, still, it can strive towards this upon better foundations than can most of the other branches of the subject. The problems which it investigates are chiefly the quantitative variations of normal processes, so that a knowledge of the extent of metabolism in health is a necessary basis. For this reason, therefore, this introductory chapter upon the physiology of metabolism is grounded upon the figures obtained from experiments, and thus necessarily precedes a consideration of the pathology of human metabolism. It is not intended as, and will not be, an original or complete study in normal metabolism, and still less in physiological chemistry, which, however, it takes more into account than it could hitherto possibly have done; its purpose is to bring together the necessary details, and to express in figures the extent of the normal processes of metabolism so far as is necessary in order to enable the reader to form an independent conception in regard to pathological processes.

It is not assumed that every figure given here can lay claim to that high degree of significance assigned it by the great physician of Heilbronn; indeed, of "lasting" value only are those which have been obtained by employing reliable, or at least the best existing methods for their determination, and by taking into consideration also all those influences which have been shown to be closely associated. By far the greatest part of the work connected with this compilation was connected with the proving and the selecting of those numerical standards which appear in the work in support of the points of view under consideration.

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[1] The German text of this volume went through the press in 1904–5. For the recent additions the Editor is responsible. The term "metabolism" is used to cover the German terms, "Stoffwechsel," the material, and "Weaftwechsel," the energy, exchange. The context readily shows whether it is the "material" or the "energy" exchange that is concerned.

I

REVIEW OF THE FOOD-STUFFS

It has been for long the custom to distinguish between the following food-stuffs:

1. *Organic Substances*, suitable for the maintenance or the increase of the total material of the body, and serving as a source of energy necessary for the execution of work and the formation of body heat.

As the principal representatives of this class of substances it is usual to mention the *Proteins*, the *Fats*, and the *Carbohydrates*. This general classification is sufficient when these substances are considered only from their value as sources of energy, but for the complete understanding of the finer processes of metabolism, of the reappearance of those substances which have taken part in the building up of the system, and of the regulation of physiological processes, it is necessary to consider individually a number of the different substances generally grouped together under these three headings. Although, on the one hand, this may be said to hold least of all for the true fats, which show no great differences in chemical constitution, on the other hand it is in the highest sense true of the carbohydrates. During the course of the last century we have become acquainted, not only with great and numerous differences in the classes of the hexoses, but also with the fact that the amido-hexoses and the pentoses are important constituents of the body. The protein group present by far the greatest differences. In this the simple proteins show marked variations in character and behaviour, and in still higher degree do the compound proteins, the nucleo-proteides, the nucleo-albumins, and the glyco-proteides, the iron-containing proteins, the albuminoids, etc., deserve a special consideration in regard to their fate during the processes of building up and breaking down which occur in the body. Formerly, when it was possible to conceive of a *general balance* in the processes of metabolism, one could remain satisfied with a knowledge of the total requirements in nitrogen-containing substances; but now, when our knowledge of the "gross metabolism" is practically complete, the investigator must turn to the more intricate study of the finer details of metabolic processes.

Besides the above-mentioned substances, the needs of the body as regards lecithin and cholesterin must be considered in a study of the nutritional processes; these occur in all animal tissues, and are systematically assimilated by the body. Further, other substances may be reviewed which are not utilized in building up the body, but instead are burnt by it, and therefore serve only as sources of energy for the body—

as, for example, vegetable-acids, amido-acids, alcohol, etc. With the exception of the last mentioned, none of these substances play an important part in the organism.

Of the principal food-stuffs, while the carbohydrates are almost entirely of vegetable origin, the fats and proteins are partly vegetable and partly mineral. The old question as to whether the protein of vegetable origin is in respect of value as a food-stuff equal to that of animal origin—whether omnivorous man, like the herbivora, could with impunity draw his entire supply of protein from the vegetable kingdom alone, is in principle one which is already decided for us through the practice of those people who live exclusively on vegetable foods. Physiological investigation can therefore only supply the evidence that it is indeed true that the vegetable-albuminous substances as they occur in nature are equal in nutritive value to an equivalent quantity of protein of animal origin (1). That a purely vegetable diet is not of advantage to the majority of mankind does not depend on any peculiar difference between the protein of plant and that of animal origin, but is the result rather of the presence of smaller quantities of the protein in vegetable food, and an unequal and unsuitable distribution of the other important food-stuffs present, as well as of certain mechanical intestinal disturbances which are often associated with a diet of entirely vegetable origin.

2. Accompanying the principal food-stuffs, which aid in the building up of the body tissues, and constitute sources of energy, there are certain secondary constituents which are either already present in the food, or have been purposely added to improve its taste. Such substances form a class of organic bodies whose part in the conservation of the tissues and in the production of heat is not an important one (the so-called flesh-extractives, the vegetable-alkaloids, the glucosides, the ethereal-oils, and the condiments or aromatics, etc.). The extractives from flesh, according to the statements of Rubner, are not broken up in the body—this has been shown to be true for creatine—although, as Frenzel has demonstrated, they undergo partial oxidation. They may, however, play some part in the maintenance of the bodily processes. The " bases " present in flesh and the condiments are, in themselves at all events, unnecessary for animal life; it was found possible, indeed, to maintain dogs in good health for months on end on a diet of flesh washed free from these substances and then mixed with the requisite quantities of salts (*Kemmerich*). Nevertheless, every " appetizer " is of extreme importance, as it imparts flavour to food-stuffs which in themselves are tasteless or insipid, and in making them edible permits systematic changes in the dietary. During their passage through the body these substances stimulate various groups of cells, specially those of the nervous system and of glandular tissues, and can thus materially affect and regulate the consumption of other food-stuffs in various ways. When not naturally present in the food, it is customary to add them thereto, and in this particular there exist marked differences of opinion between individuals as well as between the people of different races and countries.

3. Of the *Inorganic Elements*, S, P, Cl, K, Na, Ca, Mg, Fe, Si, and Mn, I, As (?) and H_2O occur in the body. They are present in food, partly

as constituents of organic substances (S, Fe, P, I), but chiefly as salts and salt-like substances. The body does not obtain energy from them—for they are practically always present in a highly oxidized state—but nevertheless they are indispensable to it. If the supply of one of these elements essential to the building up of the tissues is cut off, the organism rapidly loses ground.

In no part of the body does the protein exist in a form entirely free from ash; in all the fluids there is an approximately equal and fixed amount (as well in quantity as in composition) of mineral substances necessary in order to maintain the supply for the animal tissues. In food a certain minimum quantity (unknown in actual amount) of these mineral substances is undoubtedly necessary, but as there is always present more than this essential minimum of these substances, in health no special care regarding their addition to food requires to be taken. Common salt affords the only exception to this general rule, for in purely vegetable food, according to Bunge (3), this substance is present in smaller quantity than meets the requirements of the body.

It still remains a doubtful question as to whether these just-mentioned bodies, organic and inorganic, complete the list of substances necessary for the support of life. Various attempts to maintain animals on a mixture of chemically pure substances (albumin, fats, carbohydrates, water, and the various salts) have failed completely [Lunin, Socin (4)]. One must, however, realize that even in the simple foods—as, for example, in yolk of egg and in milk—a large number of different substances are already present, and recognise that chemistry still continues to discover in these much-studied foods certain constituents hitherto unknown.

4. *Waste Material in Food.*—With the exception of a few commercially prepared substances (sugar, etc.), all the ordinary food-stuffs contain, besides the already-mentioned materials, other bodies, partly of organic and partly of inorganic nature, which are only partially absorbed or utilized in the system. These " waste materials " in food are combined with the actual food-stuffs, and must therefore be set free during the passage of the ingesta through the intestine. They pass from the intestine unchanged, or practically so, and in a mixed diet play an unimportant part; it is only when larger quantities of bodies, such as elastic tissues, imperfectly separated tendinous tissues, bloodvessels, skin, and keratinous structures, or of cartilage, and bone, are taken into the body that they come into account as animal food. Vegetables as they occur naturally are far richer in such indigestible residues. To such residues belong in particular the older hardened forms of cellulose, the kernels and shells of fruits, and the spiral vessels of plants, structures which constitute a more or less considerable part of most vegetable foods, unless, as in the case of fine meals, they have been removed during the processes of preparation.

II

DIGESTION AND ASSIMILATION OF THE FOOD-STUFFS

A.—PREPARATION FOR ABSORPTION.

Protein.[1]

(a) *The Chemistry of the Proteins.*

In contrast to the chemistry of the fats and carbohydrates which can almost be reckoned as complete, the chemistry of the proteins is still in its developmental stages. The questions, the solution of which follow the energetic work of numerous laboratory workers, are really at present more numerous than the discoveries and results obtained. Nevertheless, our state of knowledge, in comparison with that of ten years ago, when this book first appeared, has become so much more extensive that a short synopsis of the present-day position appears necessary. Without, at least, a superficial knowledge of the chemistry of proteins, it is quite impossible, at the present day, to follow intelligently the progress of the study of metabolism, and to possess a grasp of the subject which will suffice for successful work in this field of investigation.

Among the so-called " simple " proteins, the following have been more completely analyzed : of the animal kingdom, the egg and serum albumins, hæmoglobin, fibrin and blood globulin, and also casein ; and of the vegetable world, gluten, the protein of wheat and the edestin of hemp-seed, etc.

That just those proteins which are most suitable as foods for mankind—as, for example, the proteins from animal organs and many plants —should be still comparatively uninvestigated leaves a gap in our study of nutrition, this gap being due to difficulties in the identification and isolation of these substances.

It is still a far cry to the goal of our investigations—viz., the solution of the constitution of proteins. The present efforts in connection with the chemistry of protein are all essentially directed, on the one hand, toward a determination of the nature and quantity of the smallest " building stones " (amido-acids, etc.) on which the large protein molecule is built up, and, on the other hand, to a characterizing of the greater molecular complexes (peptones, albumoses), the intermediate products from which the building up of the protein molecule in its smallest stages proceeds.

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[1] The term "protein" is used as the general name of the whole proteid group. The compound proteids are indicated by the word "nucleo-proteides." In some instances it has been thought well to retain the terms more particularly associated with certain aspects of the subject.

Not only the intermediate products, the nuclear combinations of the higher and lower orders, but also the end-products, the simple nuclei, are obtained by hydrolysis; the ferments pepsin and trypsin, and the alkalies or the various mineral acids, particularly boiling hydrochloric acid, are able to bring about these processes of hydrolysis. The action of the ferment or of the acid is based upon the same principle. The old assumption that pepsin only broke down the protein to peptones [Kühne] is refuted by more recent work; after a sufficiently long-continued peptic digestion there result quite a number of crystalline end-products, such as leucin and tyrosin, aspartic acid, together with certain peptides [Lawrow, Pfaundler, Langstein, Salaskin]. The resistance which Kühne considered to be manifested by antipeptone to the decomposing influence of trypsin is now deemed to be much less than was formerly taught. Even when auto-digestion of the pancreas is permitted to continue until the biuret reaction completely disappears [Kutscher, O. Loewi; compare also the work of Siegfried], there still remain peptides which are thrown down upon the addition of phospho-tungstic acid to the digest [E. Fischer and Abderhalden]. On the other hand, dilute mineral acids acting at low temperatures lead to the same albumoses as result from the action of ferments. When, therefore, no fundamental difference exists between the decomposing action of ferments and that of acids, it is usually preferable to employ acids for the preparation of the end-products (1) and ferments for that of the albumoses and peptones.

SCHEME OF PROTEIN FORMATION.

Protein.
(Acid-albumin.)
Albumoses (primary and secondary) } (nuclear combinations of
Peptones ("Kühne")[1] } the higher and lower
Peptoides (peptides) } orders).
"Crystalline" end-products (carbon nuclei, and elementary structures).

If we neglect the acid-albumin, the first intermediate product of acid digestion, which probably still contains the whole of the but little altered protein molecule (a splitting off of ammonia has already taken place), the albumoses are the first decomposition products to be considered. They are readily distinguished from the proteins in general by their diminished tendency to coagulation, but exhibit the protein characteristic of being easily "salted out," especially when ammonium sulphate is employed. This purely practical method of distinction, due to the school of Kühne, is, indeed, only a preliminary one; it enables, however, the drawing of a sharp distinction between higher complex substances and the simpler combinations of members of lower series. The peptones are less definitely characterized. They can neither be coagulated nor precipitated by salts; their precipitation by phospho-tungstic acid, tannin, and other reagents does not facilitate a separation from either the albumoses or the lower basic decomposition products of the proteins; they are at present identified by only one positive reaction—the biuret test. Those substances which remain after complete "salting out" by ammonium sulphate (in neutral, acid, or alkaline reaction), and give the biuret test, are called peptones. As the biuret reaction is applicable, not only for the albumoses, but, indeed, for less complex bodies also, so is the method for the identification of peptones exceedingly imperfect, and attempts to deny, or at least to limit, their existence have been repeatedly made.

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[1] It is here intended to remind the reader that Kühne's distinction between albumoses and peptones is of comparatively recent date. All works of the first eighty years of the past century, and a number of those of later years, treat of peptones in the sense of the older authors [Meissner and Brücke]; in referring, therefore, to the older works on metabolism, it must be kept in mind that every "Brücke" peptone includes the "Kühne" peptone and the albumoses of to-day.

Under the terms *peptoides* [Hofmeister] or *peptides* [Fischer] are classed a number of bodies which are derived from the peptones, but no longer give a biuret reaction. They contain several molecules of the "simple" end-products, and break down into these upon further decomposition.

Finally, the carbon nuclei cannot be further split up by the ordinary reagents for hydrolysis, but a few of the substances can be still further decomposed by the action of ferments (*vide* p. 12).

Albumoses.

The most complete investigations of albumoses have been made upon the albumoses of fibrin. The pupils of Kühne and Hofmeister have, however, demonstrated similar characteristics in albumoses obtained from other proteins. Kühne and Neumeister recognise in all three albumoses two primary—the proto- and the hetero-albumoses—and the secondary deutero-albumoses. The distinction between these bodies depends rather upon differences in solubility and the ease with which they can be precipitated than upon actual differences in structure. Since their recognition as individual substances, the number of the albumoses has still increased, and although it has not yet been possible to further differentiate the proto- and hetero-albumoses of Kühne, in the group of the so-called deutero-albumoses the presence of numerous different substances (in fibrin at least seven) has been made highly probable [E. P. Pick (2)].

These products are as yet only partially investigated, but it is fairly certain that a mixture of substances is still present. Nevertheless, they show most marked differences both in their elementary composition and in their formation from the lower groups: thus, the percentage of carbon varies from 34·5 to 55·6 per cent.; that of nitrogen from 13·7 to 18·0 per cent., while oxygen and sulphur together yield values from 19·9 to 42·9 per cent. The carbohydrate group is almost entirely absent in the majority of albumoses, being present in considerable quantity in only one, the so-called "gluco-albumose." A "thio-albumose" exists, containing a comparatively large amount of sulphur (almost 3 per cent.). The proto- and hetero-albumoses, which have been of all the most thoroughly examined, differ from each other and from the rest, as well in their unequal contents in tyrosin and the indol-forming group on the one hand, and in leucin and glycocoll on the other (the first two being present in greatest quantity in the proto-albumoses, the second two in hetero-albumoses), as in their unequal content in basic products. More recently a change in the view which Kühne held in regard to primary albumoses has taken place. Not only may the proto- and hetero-albumoses be regarded as primary decomposition products of protein: in the group of the "deutero-albumoses" (which are precipitated by complete saturation with ammonium sulphate) substances are present which are descended directly from protein, and therefore must be classed, like the "gluco-albumose," with the primary decomposition products. All these substances are obtained by peptic digestion and by the moderated action of dilute hydrochloric acid in the cold, whereas by tryptic digestion proto- or hetero-albumoses do not occur.

Peptones.

The isolation of the individual peptones (with the exception of the no longer recognised hemi- and anti-peptones), and their sharp identification, was not effected by the earlier investigators. Only within the last years has Siegfried (3) isolated several fibrin-peptones, two of which, "pepsin-peptones," are apparently identical, or, at least, pass readily from one to the other, while two others are obtained by trypsin digestion. These peptones, as well also as two from mucin and those prepared from casein, are all of acid nature. They all contain glutaminic acid, and in some of them aspartic acid, lysin, and arginin have been found.

All are carbohydrate- and sulphur-free. The peptones from fibrin contain tyrosin also, whereas those obtained by tryptic digestion no longer possess this aromatic complex. Another peptone-like product obtained by Siegfried, the glutocyrine $C_{21}H_{36}N_9O_8$, is the first peptone obtained in the form of a crystalline compound whose constitution is practically fully worked out; it results from one molecule of each of the following substances: arginin, lysin, glutaminic acid, with (probably) two molecules of glycocoll. In contrast to those already mentioned, this peptone is a strong base.

It is certain that the number of the peptones obtainable from protein is much larger than we at present know of; the less studied proteins of Pick, Fränkel, and Langstein differ from the above in many points.

The peptones are, at all events, bodies of low molecular weight. The value for Siegfried's product is less than 600, and agrees with earlier determinations, while for the albumoses five to six times, and for the proteins at least ten times, this value is accepted.

Peptoides or Peptides.

These bodies do not give a biuret reaction, and are only in part precipitated by phospho-tungstic acid. They are composed of few "carbon nuclei," and by further decomposition break down into crystalline acids and bases, amongst others leucin, glycocoll, and alanin. To this class of substances leucinimide probably belongs (see Kutscher's "Discovery of an easily decomposed leucin in the biuret-free extract of the intestinal wall"). This class of substances, whose characteristics have only been worked out within recent years, is of utmost importance for the chemistry of protein. The exact knowledge of their structure will bring disclosures of fundamental significance regarding the linkage between the carbon-nuclei of the protein molecule, and so lead to a better knowledge of the structure of proteins.

In the fibroin of silk Emil Fischer has discovered and determined the preceding stages of glycylalanin, a binary compound resulting from the union of two amido-acids (4).

More recently, Fischer and Abderhalden, by the precipitation of a pancreatic digest of casein with phospho-tungstic acid, have prepared a complex molecule of the nature of the peptides, giving the biuret reaction, and yielding a whole series of simpler bodies, such as leucin, alanin, phenylalanin, pyrrolidin-dicarboxylic acid, glutaminic and aspartic acids. This polypeptide contains six different nuclei; Siegfried's glutocyrin contains but four. Were it to contain but one molecule of each of its amido-acids, which, according to Fischer's figures, is improbable, its molecular weight would still be higher than that of many peptones. The great number of polypeptides still unknown cannot, therefore, by any means be regarded as possessing fewer or simpler combinations of nuclei than the peptones. The biuret reaction is a valuable criterion from an analytical point, but affords little light in a study of the composition of the protein molecule.

For the physiology of digestion these "peptides" are undoubtedly of importance, for they occur in no small quantity in the contents of the small intestine [Zunz (4)] (see section on Protein Synthesis).

The Simple "Carbon Radicals" or the Fundamental Substances in the Protein Molecule.

Whereas individual decomposition products of proteid—such, for example, as leucin, tyrosin, glycocoll, and others—have been long known, a large number of others have only been discovered and studied during the last ten or twenty years. With the progress which has been made in this connection the names of Drechsel, E. Schulze, Kossel, Emil Fischer, Hofmeister, Skraup, and their pupils (5) are intimately associated.

In the majority of proteins the following simple bodies have been found:

1. (*a*) *Monobasic Amido-acid sand Oxyamino-acids.*[1]—Glycocoll, alanin, serin, isoserin, amido-valerianic acid, leucine, tyrosin, and phenylalanin. (*b*) Dibasic amido-acids; aspartic and glutaminic acids.

2. *Diamido-acids.*[1]—Lysin and arginin; the last breaks down readily into cyanimide and ornithin. These substances are, like histidin (described later) of marked basic character, and therefore are precipitated by phospho-tungstic acid; by Kossel they are called hexonbases.

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[1] To 1 and 2 belong also different acids discovered by Skraup of the type of di-amidocarboxylic acids (*i.e.*, diamidoglutaric acid) and diamino-oxy-polycarboxylic acids (example, the amino-oxy-succinic acid and the tetraoxy-amino-caproic acid discovered by Neuberg and Orgler).

3. *Indol and Skatol producing Group* (*Tryptophan, Skatolamino-acetic Acid*[1] ?).—This group, along with the tyrosin and phenyl-alanin already mentioned, belongs to the three aromatic groups of the protein molecule already known.

4. *The Pyrrol Group.*—As its representatives, only the pyrrolidine-carboxylic acid and the oxy-pyrrolidine carboxylic acid are so far known.

5. *The Pyrimidine Group*, to which, according to S. Fraenkel's investigations (6), histidin[2] probably also belongs. Pyrimidine derivatives are present in great number in the animal kingdom as constituents of complex proteins, such as the nucleo-proteides (cystosin, thymin, uracil).

6. *The Carbohydrate Group* of the majority of proteins, and, in particular, of those of the so-called compound glyco-proteides, consists of glucosamine (chitosamine). According to still incomplete investigations, other carbohydrate groups are, however, present (also glucose ?) in the protein molecule. (On pentoses as constituents of the nucleo-proteides, see the section on Uric Acid and Nucleo-proteides.)

7. As *Sulphur-carrier*, cystin must be regarded as the most important ; the thio-lactic acid, which repeatedly occurs during protein decomposition, is a derivative of this body. Sulphur occurs in many proteins, as well as in cystin, and is probably present in a compound unknown at present (see Compounds of Sulphur in Urine).

Besides these substances, other decomposition products have been found resulting from the breaking up of the protein molecule, but as their presence in protein in general is doubtful, and their primary origin uncertain, they will not be here considered (NH_3, CO_2, H_2S, pyrrolidine-carboxylic acid).

The number of those substances from which the protein molecule is built up has been increased, not only by the discovery of new, hitherto unknown bodies, but also by the presence of isomeric modifications. Thus, F. Ehrlich has recently isolated a substance isomeric with the ordinary leucin, and that such cases of isomerism can influence to some extent the progress of metabolism has been suggested by Neuberg, who has succeeded in demonstrating the presence of two isomeric cystins, and has determined the difference in their reaction in the organism (6).

It has not yet been found possible to define the quantitative composition of the various kinds of protein from their elementary carbon nuclei, for even Emil Fischer's method of esterification does not admit of the complete recovery of the decomposition products. The quantitative analysis of hæmoglobin has probably been carried out more fully than that of other proteins, 70 per cent. of the original substance having been recovered and estimated in form of pure crystalline bodies. The figures for globin obtained by Abderhalden (7) may be quoted as an example of the actual proportions of the individual constituents present in such substances :[3]

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[1] According to Ellinger, tryptophan is not identical with skatolamino-acetic acid.

[2] According to Pauli, this substance has another constitution (6).

[3] Here and in similar examples it must be noted that, as a result of the absorption of the elements of water, the sum of the decomposition products of hydrolysis is larger than the original weight of the substance taken ; hence in the case of globin more than 30 per cent. of the original material has escaped estimation.

	Per Cent.
Alanin	4·19
Leucin	29·04
Pyrrollidine carboxylic acid	2·34
Phenylalanin	4·24
Glutaminic acid	1·73
Aspartic acid	4·43
Cystin	0·31
Serin	0·56
Oxy-pyrrolidine carboxylic acid	1·04
Tyrosin	1·33
Lysin	4·28
Histidin	10·96
Arginin	5·42
Total	69·87

Unequal Quantities of the Protein Radicals.

Of the many substances which go to build up the protein molecules, leucin generally constitutes the largest proportion. According to the work done by pupils of Fischer, it accounts for at least 20 to 29 per cent. of casein and globin. No other body is present in such quantity. Tyrosin occurs to the extent of from 1 to at most 4·5 per cent., and other substances, such as the generally present glutaminic acid, occur in varying amounts: in globin and serum albumin to 1·5 and 1·7 per cent., in casein to 10 per cent., and in mucedin to 19·8 per cent. Histidin occurs in like varying amounts: in most animal and vegetable proteins to a few per cent. only; in globin 10·96 per cent. consists of histidin. The proteins and the protamines, which are built up largely from basic substances, show still more marked differences in their percentage content of these simple radicals.

How closely these proteins stand in relation to one another, and what actual differences exist between individual members of the group, can only be judged first when all the decomposition products have become known and separated quantitatively. Emil Fischer points out that, according to our present knowledge, the serum albumin and globin stand in fairly close relation to one another, and that the vegetable proteins show far greater differences than do those of animal origin.

When an equal number of the same simple radicals are brought together in the form of a polypeptide, or a peptone combination, numerous polymers can result, and the number of such polymeric substances must increase the more complex the combination. Albumoses of the same nature, but of different origin, vary, as do the proteins themselves, according to the number and the nature of the union of the various substances from which the molecular complex is built up (see above). Further, if one considers that particular forms of protein—as, for example, casein, or Bence-Jones's substance—do not contain the hetero-albumoses which are otherwise usually present, and that in many proteins the of considerable importance in metabolism;—the nucleo-proteides in which albuminous substances are combined with nucleic acid, which contains phosphorus, and the nucleo-albumins,—compounds of albumin with phosphoric acid; the former contain carbohydrate groups (mostly pentoses) and xanthin derivatives (*vide* section on Uric Acid). In the glyco-proteides (mucin, ovomucoid, etc.) the protein is present in combination with particularly large amounts (up to 35 per cent.) of carbohydrates (chiefly glucosamine); in hæmoglobin it is combined with iron containing pigments. These bodies will be briefly discussed in other sections of this book; it is here sufficient to point out that the albuminous half of the molecule of these compound albumins is readily separated from the combination (Kossel's "prosthetischen Gruppe"), and by the further action of acids[1] or ferments[2] the same albumoses and peptones are obtained as from the simple proteins themselves. In the digestive tract the breaking down of the albuminous constituents of the *compound proteides* proceeds, at all events, in a fashion analogous to that of the simple albumins [Umber].

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[1] For example, by hæmoglobin.

[2] This is known at least for casein and for the pancreatic nucleo-proteid.

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1. THE DIGESTION OF THE PROTEINS.[1]

(a) Protein Digestion in the Stomach.

With the exception of milk and raw eggs proteins are usually taken by man in coagulated form. About fifteen minutes after their entrance into the system the products of their digestion (substances giving the biuret reaction) are to be found in the stomach [Ewald and Boas]; syntonin, albumoses, and peptones are here formed [Zunz, Reach, in dogs], and the splitting up of the protein molecule in the stomach proceeds still further than to peptones. Along with the albumoses, which always preponderate, peptones occur in small quantity [Ewald and Zunz], and their presence in the human stomach after a diet of egg-albumin has been proved by Chittenden; peptoides not precipitated by phosphotungstic acid are also met with here [Emerson (1)].

Absorption in the Stomach.—A large accumulation of the products of digestion does not usually take place, since only a small quantity of the total albumin in the stomach is acted on at one time, and even in the last stages of digestion (after twelve hours), in that of flesh particularly, unaltered albumin has been found in the stomachs of dogs and pigs [Schmidt-Mühlheim, Ellenberger, and Hofmeister (2)].

The soluble products of digestion pass fairly quickly from the stomach towards the intestine, but an absorption of albumoses and peptones in the stomach as well also as one of peptoides has been confirmed [Aurep, Brandl, Tappeiner, Mering, Zunz, Reach].

With the taking up of these predigested products the absorption in the stomach amounts to about 2 to 13 per cent. of the total quantity of protein introduced—viz., a few grammes in weight. Addition of alcohol increases the rate of absorption [Brandl (3)].

The amount of undigested albumin absorbed by the human stomach cannot therefore be called extensive.[2] Moritz has shown that in the stomach of dogs during a space of seven hours only insignificant quantities of the nitrogen of flesh, and practically none of the proteins of milk, are absorbed.[3]

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[1] It is not necessary here to consider the mechanism of absorption at all fully. The sections upon "Carbohydrate and Fat Metabolism," by J. J. Macleod, and upon the "Mechanism of Absorption," by A. P. Beddard, in Leonard Hill's "Recent Adventures in Physiology and Bio-chemistry" (London, 1906), include all the recent work and the references to English and American authors, and to this the reader is referred.

[2] It may be incidentally noted here that water is not absorbed at all in the stomach (Mering), or, at least, that any absorption is concealed by a still greater separation of this element.

[3] Consult also Grützner, *Pflüger's Archiv*, vol. cv., and Tobler, *Z. f. Phys. Chemie*, 1905, vol. xlv.

The Stomach as a Reservoir.—Besides the functions of digestion and disinfection which the stomach performs, one of its principal duties is to act as a reservoir from which the intestine may be continually supplied with the food material which is capable of being utilized. One finds, therefore, that food remains some considerable time in the stomach; 500 grammes of flesh have not completely disappeared from the stomach of a dog or of a pig after twelve hours [Schmidt-Mühlheim, Ellenberger, and Hofmeister], and the period during which the food remains in the stomach of the human being cannot be assumed to be less than such period. According to experimental work on this subject by Leube, a test meal, considerably less in quantity than what might be considered a normal dinner, disappeared entirely from the stomach only after a space of seven hours (3).

The Rennet Ferment, or Rennin.—The rennet-ferment[1] chymosin, which is secreted from the mucous membrane of the stomach, not only has the property of coagulating milk protein, but also of partially throwing down the albumoses (specially the secondary A and B albumoses) from their solutions [Danilewsky, Okouneff, Sawjalow]. This "plastein" formation was originally held to be a rebuilding of protein from albumoses and peptones, and the synthesis of the tissue protein from that of food was attributed to this rebuilding action of the rennet ferment. This is not in harmony with our modern views regarding protein formation, for it is generally held that it results, not from "peptones," but from crystalline products.

Lawrow and Salaskin, and also Kurajeff and Baeyer, have recently shown that "plastein" is by no means a substance of the nature of protein, but an albumose or peptide. The fact that chymosin occurs in parts where its action on the protein of milk cannot come into account warrants the belief that it possesses other important properties besides that of precipitating casein. Rennin is to be found in the testicles of mammals, in the stomach of birds, fishes, frogs, and is scattered widely in the vegetable kingdom (3A).

(*b*) Protein Digestion in the Small Intestine.

The ordinary mixed foods pass slowly into the duodenum and jejunum in the form of semiliquid masses. More than a certain small amount never enters, and the duodenal mucosa is generally covered with a thin layer of soft chyme. Pure water is the only substance which leaves the stomach quickly in large gushes [von Mering Moritz (4)], and this only when the small intestine is empty; meat-broth and milk may, however, occasionally do so. [In dogs (Moritz), and in man (C. A. Ewald).]

The passage of the stomach contents into the jejunum produces a reflex closing of the pylorus, the action being a chemical rather than a mechanical one. When the chyme is of acid character it produces a temporary, but advantageous, closing of the stomach [Lintwarew, Serdjukow]. According to these authors acid contents in the stomach pass the most slowly into the intestine, neutral contents emerge at a somewhat quicker rate, while alkaline chyme is discharged the most quickly of all. The results of human pathology in regard to the increase of motility in conditions of deficient acidity and lessened motility in hyperchlorhydria stand in complete harmony with the observations of experimental physiology (4).

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[1] Pawlow disputes the existence of an individual rennet ferment.

Ferments and Protein Decomposition in the Small Intestine.

Along with the liquid contents of the stomach small soft masses and tiny solid particles pass into the small intestine [Moritz], and in the later stages coarser fragments of material incapable of being thus further broken up are expelled from the stomach. Along with this undigested material the intestine also receives from the stomach for further treatment quantities of undissolved and dissolved protein, albumoses, and peptone. Now the presence of the nitrogen-containing chyme in the small intestine is due to the powerful decomposing influence of trypsin, which decomposes all proteins with the exception of raw connective tissue;[1] its action is aided considerably by the presence of the ferment erepsin in the mucous membrane of the small intestine [Cohnheim]. This latter ferment decomposes none of the proteins except casein [Cohnheim, Salaskin], or at least only to a slight extent [Kutscher and Seeman, and several older authors]. On the other hand, it breaks down the albumoses and peptone completely to crystalline products. These statements also hold for human intestinal juice [Demant, Tubby-Manning, Nagano, Hamburger-Heckma]. Erepsin not only occurs in the walls of the intestine, but is also to be found, although less active, in the intestinal juice itself [Salaskin (5)], and in the tissues generally. The action of trypsin is but little augmented by the biliary secretion; entero-kinase, however, a substance which is present in the intestinal fluids, quite apart and distinct from erepsin, powerfully supplements tryptic digestion [Schepawolnikow, Pawlow (6)]. According to recent statements by Lintwareff, this effect is entirely due to increased activity of the trypsinogen. The active principle of the pancreatic juice is in dogs secreted, except when on a purely flesh diet, as trypsinogen, the precursor of the ferment trypsin. Glässner has also found (6, *a*), in the only cases in which it has been possible to obtain normal human pancreatic secretion, that trypsinogen only, and not trypsin, is present; he could produce proteolytic activity, however, in the former by means of human entero-kinase, although not by that obtained from dogs. The nature of the decomposition of protein in the course of normal digestion, produced by pseudopepsin [Glässner] and by the ferments of the so-called Brunner's glands, is not yet sufficiently known (6, *b*).

By the united action of the various ferments a powerful proteolytic decomposition takes place in the small intestine. Although undissolved protein may still exist far down the intestine—indeed, in the cæcum—[Nencki], nevertheless dissolved protein capable of coagulation by heat is also to be met with, originating partially, no doubt, from the juices of the pancreas and intestine. Substances giving a biuret reaction (albumoses and peptone) have practically always been identified in animals and also in man [Schmidt-Mühlheim, Ellenberger, and Hofmeister, Nencki, Jakowski, A. Schmidt]. The true albumoses, according to Kutscher and Seeman, occur only in small quantity, and Zunz maintains that they always contain a very great portion of the dissolved nitrogen (in the early stages of digestion up to 94 per cent., and in the later only 32 per cent.).[1] True peptone was met with only in small quantities [Neumeister, Kutscher-Seeman, and Zunz (F)].

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[1] This is only acted on by pepsin-hydrochloric acid; in "achylia gastrica," when raw flesh is consumed, connective tissue occurs in considerable quantity in the stools.

Of fundamental importance is the occurrence in the small intestine of certain products of proteolytic decomposition of a lower order than the peptone. The older statements regarding the presence of leucin and tyrosin in the small intestine of man [Kölliker and Müller] and of animals [Kühne, Sheridan-Lea] have been lately confirmed by Kutscher and Seeman (8). These positive results are more important than the negative ones of Schmidt-Mühlheim, of Nencki and A. Schmidt; that these last authors could no longer detect the presence of such substances in the intestinal contents from an ileo-cæcal fistula can be explained by the probability of the already complete absorption in the small intestine; lysin and arginin have also been here found by Kutscher and Seeman. The number of the crystalline products of protein decomposition in the intestine will almost certainly increase as research in this direction advances. The sum of the nitrogen-containing products of a lower order than the peptone is undoubtedly very large in the case of dogs, for Zunz has shown that in the last stages of digestion upwards of 56 per cent. of the total soluble nitrogen can no longer be precipitated by phosphotungstic acid (8).

The small intestine remains charged with the pulpy products of food in process of digestion for a much longer period than the stomach, for the intestine is continually receiving fresh quantities of material by each successive contraction of the latter. Of interest, however, is the question in what time the individual particles thrust out from the stomach pass through the small intestine. Nencki detected the presence of legumen at the ileo-cæcal valve about two to five hours after a diet of the same, and the last traces were ejected from the stomach only after fourteen hours. A. Schmidt reports a similar case in which the first portions of the product of a " light " breakfast appeared in the excrement from the fistula after three hours, and the last portions after six hours, and Ewald, by means of a fistula about the middle of the small intestine, detected the presence of liquid foods, milk, and the broth from meat soon after their entrance into the system (9).

Reactions.—The reaction of the contents of the small intestine, according to the majority of investigators, is faintly acid in the upper portions. The acidity decreases as the cæcum is approached, and the reaction may even become alkaline. This is true for animals and also for man [Nencki] on a mixed diet [Ewald], and on an excess of animal food [Matthes and A.

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[1] By feeding simultaneously with boiled meat and the broth from the same digestion proceeds further than without this.

Schmidt (10)]. The faintly acid nature of the chyme, despite the influx of considerable quantities of alkali with the intestinal and pancreatic juices, is due to the presence of weak acids—the lower fatty acids such as acetic acid [Nencki], the higher fatty acids [Pfluger]—or to carbon dioxide [Matthes].

The choice of an indicator is of importance. The same intestinal contents which react alkaline to methyl-orange or litmus may show an acid reaction with phenolphthalein and rosolic acid. Matthes and Marquardtsen have found that litmus reacts acid to the upper and alkaline to the lower portions of the intestinal contents (10).

Absorption in the Small Intestine.—The greatest absorption of nitrogen-containing food-stuffs as well as of all other food constituents takes place in the small intestine. According to Lannois and Lépine (11), a larger absorption of peptone, sugar, and oil occurs in the upper reaches of the small intestine than in the lower, and in a series of experiments Nencki found that on mixed diet only 10·6 grammes (=14·25 per cent.) of the original 70 grammes of protein ingested appeared at the human cæcum, so that 60 grammes (=85 per cent.) had been absorbed in the small intestine. Honigman obtained similar values (1·9 to 2·9 grammes N.) in the total daily ileo-cæcal excrement on a diet rich in protein (11).

In what form the nitrogen-containing constituents of food are absorbed in normal conditions is still undecided. The older view which held that protein could be only absorbed when reduced to the state of a peptone is refuted by the statements of Brücke. Numerous experiments introducing protein bodies (myosinogen, egg-albumin, and casein) into the rectum have shown conclusively that an absorption of natural protein takes place in the rectum and colon (12). Here, however, it is quite possible that the descending pancreatic ferments produce a partial decomposition, and so cause an absorption of the protein introduced. The experiments on the separated loop of small intestine are more conclusive, for then only the ferment erepsin is present, and it has no action, or at least a very slow one, on true protein. These experiments serve to show that the protein of flesh, the serum and egg albumins are absorbed as such [Voit and Bauer, Heidenhain, Friedländer]. The possibility of the absorption of unchanged protein in the intestine is thus well grounded. This absorption of protein is probably only of practical account in the case of protein arising from the processes of the body in connection with the secretion of the intestinal and pancreatic juices into the intestine, because it has been found that trypsin but slowly attacks the similar protein of the blood [Oppenheimer]. It appears to be otherwise with the food protein. The absorption of dissolved protein proceeds so very much more slowly than that of albumoses and peptone [Röhmann, Cohnheim] that it cannot be considered to play any important part in physiological processes. Only the passage of raw egg-albumin into the blood and the urine seems to be certain [Ascoli (12)]. The fact that albumoses and peptone are always present in the intestine, in spite of their rapid absorption and further decomposition, points to a continual new formation of these substances; such a process can hardly be deemed unnecessary, and therefore, if protein is absorbed at all as such, it can only be in mere traces, the larger quantity being decomposed first, and then absorbed in the forms of simpler bodies. According to recent investigations by Cohnheim, Kutscher and S. Seeman, and Loewi (13), not even the albumoses and peptone are absorbed, but "biuret-free" substances only [peptoides and crystalline bodies]. As to the physiological importance of protein decomposition, see the section on the Synthesis of Proteids.

Hoppe-Seyler was the first to suggest that the absorption of food material is not a simple physical process of diffusion, as it was thought to be some fifty years previously, when the various branches of the sciences were brought to bear on physiology, and his teaching was afterwards extended in various directions and confirmed by Heidenhain (14). The latter investigator pointed out that water was taken up from the intestine from a dilute solution much more rapidly than the dissolved substances contained in it, and that absorption also took place when no difference in osmotic pressure existed between the intestinal contents and the blood which was absorbing them. With an aqueous mixture of grape-sugar and sodium sulphate the sugar disappeared from the intestine very rapidly, the sulphate much more slowly [Röhmann]. Absorption is due to the activity of the epithelial cells, which abstract—like the fine hair-roots of plants—from the nutritious chyme those products which are most suitable to them (14).

The Paths of the Absorption of Protein.—The bloodvessels form the chief path for the passage of the protein into the body; the lymphatics do not carry digested protein. Schmidt-Mühlheim (15) has shown that quite as much protein disappeared from the intestine of a dog when the thoracic duct was ligatured as in a normal animal. Munk and Rosenstein were able to estimate the amount of protein in the chyle issuing from a lymph fistula in the case of a girl, the quantity determined during the eleven hours following a diet of 500 grammes of flesh not exceeding the amount yielded during a period of fasting. More recent experiments by Asher and Barbèra would seem to limit this statement, however, and tend to show that a partial transportation of nitrogen into the lymphatics actually takes place. Mendel, in repeating their work, could not confirm these results, and J. Munk has calculated that in the experiments of Asher and Barbèra, at least 92 per cent. of the nitrogen must have found its way into the body through the bloodvessels (15).

(c) The Function of the Large Intestine.

The chyme passes from the small into the large intestine in a regular stream; an almost continual flow of excrement was obtained through a fistula at the ileo-cæcal valve. The chyme is usually excreted in a semi-liquid condition, but may sometimes form a thick pulp. It contains from 90 to 95 per cent. of water, and has no fæcal odour. Nencki (16) observed the passage of 250 to 530 c.c., and Jakowski of 200 to 300 c.c., of chyme during twenty-four hours through the cæcal fistula of patients on mixed diet. The thickening or concentration to the normal quantity

(100 to 150 grammes) of excrement passed as fæces occurs, therefore, in the large intestine. The function of the colon is, therefore, to complete the digestion and absorption of the food materials, particularly that of water; it does not secrete a tryptic ferment with a specific action on proteins. Nevertheless, under the influence of enzymes carried down from the upper intestine, an "after-digestion" [A. Schmidt] of still undecomposed protein residues probably occurs. In human fæces, after separation of the bacteria, Hemmeter was able to demonstrate a ferment of the nature of trypsin (16).

(*d*) Decomposition of Protein by Bacteria in the Intestine.

Besides the decomposition of protein produced by digestive ferments in the intestine, the concurrent action of bacteria must be considered. The micro-organisms utilize at least a part of the protein for their individual requirements, but they decompose the remaining portion so completely that it becomes unavailable for their assimilation. In so far as the products of protein decomposition by bacteria are the same as those produced by enzymes (leucin, tyrosin, etc.), it is impossible to estimate the extent of the decomposition produced by the former. Nevertheless this process is not detrimental, for the decomposition products are of the same value to the body whether they are produced by the bacteria or by the enzymes of the intestinal tract. The earlier conception, whereby the simple substances resulting from the breaking down of protein in the intestine were produced only by bacteria, their occurrence therefore denoting a loss to the body, has been shown to be incorrect. The extent of proteolytic decomposition produced by bacteria must not be overestimated. In artificial cultures only a small quantity of the food materials, even after superabundant inoculation, is decomposed by the bacteria, and the quantity of decomposition products is small, even when the medium is present in excess. Through absorption by the intestine the greater part of the food-stuffs therefore escape the slow action of the bacteria.

Pasteur and Duclaux agreed that the presence of bacteria in the intestine was necessary to normal life, but Nencki held such a symbiosis between the parasites and their host as improbable (17). Experimental investigations have not yet satisfactorily decided this point.

Nuttall, Thierfelder and Schottelius, by experimenting on various animals (guinea-pigs and hens), obtained contradictory results. Should, in the sense of Pasteur, a symbiosis with micro-organisms be essential by the higher animals, then finer chemical changes ought to indicate the same rather than the rough quantitative relations which result from the decomposition of the food-stuffs. Metchnikoff opposes the view that the lower parasites in the intestine are useful or essential to life. According to him, the products of putrefaction produced by these parasites bring about the premature aging of their host and shorten his life. Of such decomposition products of protein produced exclusively by the action of bacteria, and not by that of the unorganized ferments, skatol and indol, phenol and cresol (and urobilin) are best known. Although the systemic

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origin of these substances is still vigorously discussed, so much is nevertheless certain—namely, that they are largely due to the activity of bacteria [Baumaun, Nuttall, Thierfelder, etc.] (compare the chapter on the Aromatic Bodies in Urine). The classic research of Jaffé and Nencki has shown that these bodies are not present in the small intestine [confirmed by A. Schmidt and others]. They originate, therefore, in the large intestine, in which the micro-organisms have the necessary time to produce abnormal decompositions. This fact has become of importance for the recognition of many intestinal troubles, but the actual reasons for this difference in behaviour of the bacteria in the large and in the small intestine have not yet been satisfactorily explained [A. Schmidt (17)].

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2. THE DIGESTION OF THE CARBOHYDRATES.

During the last twenty years the advances in our knowledge regarding the carbohydrates has extended the circle of sugar-like substances which are of importance in a study of nutritional processes. Pentoses are contained in the pentosanes and nucleo-proteides, and a new source for hexoses has been discovered in the sugar-rich glyco-proteides and in most of the other common proteins. The chief form of carbohydrate utilized in the body is free hexose. It is present in the vegetable kingdom in starch, dextrin, cane-sugar, grape-sugar, and fructose, and, in the animal kingdom, in smaller quantities as glycogen and milk-sugar. It is taken up as food in either a simple or a polymerized condition.

Only the monosaccharides, grape-sugar, and lævulose are absorbed as such. The insoluble or sparingly soluble polysaccharides (starch, glycogen) become soluble through the action of ferments in the digestive tract, and are decomposed into simple sugars. In a similar manner the disaccharides (cane-sugar and milk-sugar) undergo a process of splitting up of the molecule in the digestive tract. The saliva, the pancreatic secretion, and the succus entericus take part in this process on account of the ferments which they contain. The bile, which acts apparently as a coadjutor to the pancreatic juice, possesses no amylolytic properties. The gastric juice acts only on the cane-sugar.

The hydrolysis of starch and glycogen to soluble starch (amidulin or amylodextrin), erythro- and achroo-dextrin, iso-maltose and maltose, and finally to dextrose, is brought about by two different ferments—*ptyalin*, which reduces starch to maltose; and *maltase*, which converts the latter into dextrose.

The saliva and the pancreatic juice have a diastatic action. They split up starch into maltose, and form but little dextrose (saliva produces about 1 per cent. of dextrose); succus entericus, on the other hand, decomposes starch only slightly, maltose vigorously and with ease.

Digestion and Absorption in the Stomach.—Starch is usually ingested after having been first broken up and partially reduced to dextrin by cooking or baking; it is seldom eaten in its raw state. The saliva is the first digestive juice which acts upon the starch, and an amylolytic decomposition occurs even during the short period in which the food remains in the mouth. The amylolytic process continues in the stomach until the ever-increasing acidity of the contents puts an end to the further action of the saliva. According to v. d. Velden (1), it is the appearance of free HCl which makes ptyalin inactive; the presence of 0·1 per cent. HCl ends its activity in test-tube experiments [Chittenden]. In a "test" breakfast, therefore, the greatest digestion of starch takes place in the first half-hour [Ewald and Boas, Johannes Müller (1)]. With a "test" dinner, in which free acid appears first much later, the transformation of starch continues much longer [v. d. Velden]. Reducing substances (dextrin, maltose, dextrose) are formed in the stomach in only small quantity [to 0·5 per cent. of the stomach contents, Ewald and Boas, Strauss]; non-reducing dextrins, in particular achroö-dextrin, form the chief decomposition product. J. Müller found in the stomach, fifteen minutes after ingestion of a semiliquid diet, 60 to 80 per cent. "dissolved" carbohydrate, and 20 to 90 per cent. after a diet of bread. In conditions of diminished acidity, or in achlorhydria, the solution and digestion of carbohydrate proceeds further than in normal acidity [Strauss, J. Müller], and when the acid contents are prematurely present in excess the amount of solution of starch falls to 36 per cent. [Müller (1)].

Absorption in the Stomach.—The normal extent of absorption of the formed soluble products by the human stomach is still not determined. From experiments on animals, however, it has been ascertained that, when the stomach is closed with a tampon or ligature, sugar is certainly absorbed, but never in any quantity except from concentrated solutions [Aurep, Tappeiner, Brandl, v. Mering (2)]. This has also been proved to hold for the human stomach in its ordinary state by the interesting experiments of Mering (sugar with fat emulsion). The absorption from weak solutions is, however, but slight, and as the normal stomach only produces but small quantities of the reducing sugar from starch, and as the absorption of maltose and dextrin which preponderate here is much less than that of dextrose, the belief that any more vigorous absorption of the derivatives of starch can take place in the stomach under the ordinary conditions of dietary is not justified (2).

The Carbohydrates in the Small Intestine.—The small intestine is the chief place for the digestion and absorption of carbohydrates. The pancreatic juice, which contains, along with small quantities of maltase, ptyalin in considerable amount, is aided by the succus entericus, in which these two ferments are present in an inverse ratio. The complete decomposition, therefore, of any starch which may have been partially digested or may have escaped decomposition entirely in the stomach is quickly brought about in the intestine. It is not yet known with certainty whether maltose as well as dextrose is absorbed as such from the intestine, but this is possible, since all the organs contain a ferment capable of decomposing maltose [Röhmann, Bial (3)]. This ferment would therefore tend to bring about a decomposition of the maltose absorbed.

The Soluble Saccharides.—Cane-sugar, the chief sweetening medium of civilized man, is ingested not only in a pure state, but also in many fruits. It is partially decomposed by the free hydrochloric acid in the stomach [Leube, Seegen (4)], and in the pancreatic juice a ferment is present which splits it up into its components. Köbner and K. Voit and their students have succeeded in tracing its decomposition in the intestinal tract of dogs and rabbits to the far-reaching stages of dextrose and lævulose. An inversion has also been found [Demant, Nagano, Tubby, and Manning (4)] to take place in the succus entericus of man, but according to Nagano and Röhmann, cane-sugar is but slightly decomposed in the intestinal lumen, and first only to any considerable extent in the intestinal wall itself. That it must be decomposed in order to be assimilated by the body, and that it is in reality fully broken up when introduced into the intestine in not too large quantities, has been made highly probable by the work of C. Voit and his pupils. As soon, however, as a quantity is introduced into the body in excess of that which is capable of being absorbed in an undecomposed condition by the intestine, just as when it is introduced subcutaneously, it appears again unchanged in the urine [Fritz Voit (4)]. No other part of the organism except the intestine contains an enzyme capable of decomposing cane-sugar.

The same holds true for lactose or milk-sugar. The ferment lactase, which is responsible for the breaking up of lactose into dextrose and galactose ~~maltose~~, is absent, however, in the succus entericus of all animals and of man [Tubby and Manning]. Hence K. and F. Voit (5) found only milk-sugar and none of its decomposition products in the intestinal contents of full-grown rabbits. The ferment lactase has been described as occurring in the mucous membrane of all mammals during the lactation period, and also in most of them after weaning [Fischer and Niebel, Röhmann and Lappe, Weinland, Orban, Röhmann and Nagano (5)]. The decomposition of milk-sugar does not therefore occur, like that of other carbohydrates, in the cavity of the intestine, but in the wall of the same. It has not been possible to isolate a lactase from the mucous membrane of rabbits, and in these animals the decomposition of the milk-sugar seems to be performed by the living cells. If milk-sugar is introduced subcutaneously, or should it be present in such quantity that it passes the mucous membrane of the intestine undecomposed, then it appears again in full quantity in the urine [C. and F. Voit]. Like cane-sugar, it is not broken up by the general tissues of the body (5).

Maltose and iso-maltose occur in beer, and are absorbed largely as dextrose.

Dextrose or grape-sugar is present in many fruits, either as the predominant sugar, as in grapes, or along with an equal quantity of lævulose. Honey is particularly rich in lævulose. The monosaccharides are absorbed as such, and, like maltose, are used up by the body on subcutaneous injection, and do not reappear in the urine [F. Voit].

Glycogen is utilized to a slight extent by the liver and muscle of animals. Its decomposition and absorption are similar to that of starch.

Cellulose is decomposed by bacteria in the intestine. It is not acted on by digestive secretions, but it disappears almost entirely from the intestine of herbivora and, in not inconsiderable quantities,[1] from the intestine of man, when introduced in a finely divided form [Weiske, Knieriem, Konstantinidi, and others (6)]. Gases and volatile fatty acids are products of its fermentation [Tappeiner and others], but it has not yet been found possible to isolate sugar-like intermediate products from this bacterial decomposition [A. E. Müller], although their occurrence is nevertheless probable [Henneberg and Stohman]. The products of the fermentation of cellulose and sugar are largely absorbed by and oxidized in the body, and when hundreds of grammes of cellulose disappear in the intestinal tract, as is the case in herbivora, only small quantities of acids, representing a few per cent. of cellulose, appear in the urine and fæces [Wilsing], while along with these large quantities of methane are excreted through the lungs. Hence either sugar must be produced from the cellulose and taken up by the body, or acids are formed (along with the gases [H, CH_4]), which are absorbed and oxidized. The oxidation of these acids supplies to the body, nevertheless, a quantity of energy not far short of that obtained from sugar (6).

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[1] The estimation in the fæces is often unreliable [Mann (6)].

The Function of the Large Intestine.

The digestion and absorption of the carbohydrates is carried out almost completely in the small intestine. Macfadyen, Nencki and Jakowsky found in the case of man that only very little starch or sugar appeared in the intestinal contents obtained from an ileo-cæcal fistula, and Ewald and Adolf Schmidt could not detect sugar at all in a similar case (7). The large intestine is also capable of acting upon starch, and of absorbing the sugar-like products of its decomposition, so that it can always, without difficulty, perform any work which the small intestine may have left for it to do.

The absorption of the various forms of sugar in the intestine proceeds with unequal velocity. This observation, whch has been made repeatedly on animals [Weinland] has, by means of a Thiry's fistula, been found to hold good for man [Nagano (8)]; maltose and dextrose disappeared completely in one hour, whereas only 26 per cent. of milk-sugar, present originally in equal quantity and in the same concentration as the maltose and dextrose, was absorbed during the same period. The reason of this lies in the fact that the first-named sugars pass readily through the intestinal epithelia without first undergoing a further change, whereas a certain interval is necessary for the decomposition of milk-sugar in the cells, during which time no more material is taken up by them. This is true for cane-sugar [Röhmann, Nagano] and for the other sugars as well [Nagano (8)]. A selective activity of the cells during absorption, which has been suggested by Hoppe-Seyler, is no doubt true for the absorption of those carbohydrates which are soluble in water. This activity of the cells, which, after all, must be due to chemical and physical forces, cannot be explained either by the processes of diffusion or absorption with which one had formerly exclusively to deal; the new teaching, on the other hand, in regard to the conditions of osmotic pressure, seems to further considerably the solution of these vital processes.

The Paths by which Carbohydrate is carried from the Intestine.

The lymph of the thoracic duct is not richer in sugar after a diet of starch or sugar than during the condition of hunger [v. Mering (9)], and the blood-stream therefore carries off the sugar absorbed. Accordingly, the serum of the blood obtained from the portal vein after carbohydrate diet is richer in sugar than that of carotid blood (0·31 to 1·23 per cent. [Bleile]). Munk and Rosenstein succeeded in confirming this for man; after a diet of 100 grammes of starch or sugar only 0·5 gramme at most of dextrose was removed in nine hours' time via the lymph-stream. Only when an excess of grape-sugar is present in the intestinal tract do small quantities pass into the lymph-stream. In such cases the sugar contents of the chyle of rabbits is increased from 0·24 to 0·49 per cent., and a similar condition is met with in dogs [Ginsberg (9)].

The Decomposition of Carbohydrates by Micro-organisms.

The carbohydrates yield to the attack of micro-organisms just as does protein. They break down through fermentative processes into lactic acid, acetic acid, butyric acid, formic acid, and alcohol [Macfadyen and Nencki, Jakowsky, A. Schmidt (10)]. The extent of this decomposition in the intestine escapes quantitative estimation, but nevertheless it must remain within moderate bounds. These fermentation processes play a certain part in the evacuation of the bowels, in so far that acids in considerable quantity tend to assist the emptying of the intestine, as the experiences by dieting on sour, doughy bread serve to show.

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3. THE DIGESTION OF FATS.

The greater part of the fats consists of glycerine esters of oleic, palmitic, and stearic acids; 100 parts of fat yield on saponification about 95 per cent. of fatty acids and 10 per cent. of glycerine. About 2 per cent. of glycerides of lower fatty acids, in particular of butyric acid, are present in butter along with the more important fats, and besides these, the presence in small quantities of the various acids with an equal number of carbon atoms—from butyric to stearic—has been confirmed. Small quantities of free fatty acids (rancid fat) occur frequently along with the glycerides, not only in vegetable, but also in animal fat, in particular in cod-liver oil. In certain foods—as, for example, in milk, cream, or the yolk of egg—the fat is consumed in the form of an emulsion, but as a rule fat enters the stomach in an either liquid or half-solid condition. For the digestion of fat the masses of insoluble fat must be broken up into small particles, emulsified, and decomposed. The fat-splitting process is carried out by the steapsin ferment, which is present in the gastric and pancreatic juices. The bile and the succus entericus do not contain the steapsin ferment, but they aid, nevertheless, in the digestion of fat on account of the emulsification which they produce.

Digestion of Fat in the Stomach.

The presence of the steapsin ferment in the stomach was first confirmed by Marcet. Its presence, overlooked or denied by most [only recognised by Cash, Ogata, Klemperer, and Scheuerlen], has been lately identified in the gastric juice of dogs and in that of man [Volhard (1)]. Numerous experiments show that about 78 per cent. of the fat contained in an emulsion of egg-yolk can be broken up. This enzyme, however, does not come much into action under normal conditions, for liquid fat does not undergo emulsification when the stomach contents are acid in reaction; since the fats in egg or in milk may remain in a state of emulsion for some time, the decomposition of the fats in these substances proceed further than in others. At the height of digestion, emulsification is to a great extent prevented by the pepsin-hydrochloric acid, and the action of the ferment is therefore lessened or entirely inhibited.

The stomach acts as a reservoir for fat just as for protein, and allows only that amount of material to enter the small intestine that can be advantageously utilized by it. Thus Zawilski (2) has found in the stomach of dogs (weighing 13 kilogrammes), after they had been fed on a maximum quantity of fat (150 grammes), that 108 grammes of the fat was still present in the stomach at the end of four hours, 98 grammes after five hours, and 9·7 grammes at the end of twenty-one hours, whereas in the small intestine after the same intervals 9·9, 8·8, and 6·2 grammes were found, so that practically equal quantities of fat were present throughout. The experiments made by Pawlow's students serve to show that the closing of the pylorus, with the consequent cutting off of the flow of the fat to the intestine, follows the direct contact of the fat with the mucous membrane of the small intestine.

Digestion of Fat in the Small Intestine.

The preparation of the fats for absorption only really commences after they enter the intestine. The process there is a normal one produced by the combined action of the bile and the pancreatic juice with the aid of the succus entericus. That both these two juices are necessary is best shown by experiments on animals in which the pancreatic juice and the bile are made to pass into the intestine separately, and at different points. In rabbits the pancreatic duct pours its contents into the intestine 35 cm. below that of the bile-duct. Only those lymphatic vessels (the channels for fat absorption) which lie below that part of the intestine at which the bile enters the same are filled with fat, and the section of the intestine lying between the pancreatic duct and the bile-duct does not take up fat [Claude Bernard]. The reverse state of affairs is shown in the striking experiment of Dastre, which forms a supplement to the work of Claude Bernard. Dastre connected the gall-bladder with the small intestine about ½ metre to 1½ metres lower down, and having ligatured the lower end of the bile-duct, found that no absorption of fat took place above the point at which the bile entered the intestine. Other experiments on animals, and pathological investigations in connection with man, show that the combined action of the bile and the pancreatic juice is necessary for the absorption of fat. C. Voit, Röhmann, and Fr. Müller (3) found that when the bile is cut off completely from the digestive tract a large fraction of the fat taken into the stomach is no longer absorbed (40 to 58 per cent. in dogs, and as much as 78 per cent. in man). The statements bearing on the behaviour of fats after the exclusion of the pancreatic juice vary very much in regard to man. Complete extirpation of the pancreas from dogs is followed by the absorption of 33 to 45 per cent. of non-emulsified fat [Abelmann, Sandmeyer], although 80 per cent. of emulsified milk-fat may still be absorbed by the intestine [Abelmann (4)]. This long unexplained phenomenon of the better utilization of emulsified fat has been made clear by the discovery by Volhard of a steapsin ferment in the stomach. If the connection between the pancreas and the intestine is completely and permanently cut off, the pancreas itself still remaining wholly or partially in the system, it is found that the absorption of fat may be maintained (80 per cent.) for a considerable length of time [Sandmeyer, Abelmann, Rosenberg]. No other explanation of this fact can be given at present, except that the steapsin of the still active pancreas is taken up by the lymph- and the blood-streams, and carried to the intestine to complete its function there. This is the probable explanation of those cases in which, in spite of an obstruction in the pancreatic ducts, fat is digested and utilized [Fritz Müller]. In other instances in which the occlusion of the pancreatic duct has been proved anatomically, from 53 to 83 per cent. of the fat appeared in the fæces [Deucher (4)]. At all events the importance of the human pancreatic juice for the digestion of fat has been definitely proved by therapeutic investigations in spite of many statements to the contrary. In steatorrhœa, which Hirschfeld has shown to occur in diabetics, it has been found possible to partially restore the power of utilizing fat by administering pancreatic extract. In experiments conducted by H. Salomon it was found that a loss of from 51 to 53 per cent. of fat fell to 17 to 19 per cent. after administration of pancreatic substance and pancreon (4).

The absence of an acid reaction, or the absence of " free " and " combined " hydrochloric acid, is of advantage for the decomposition of the fats. This condition is secured in the small intestine by the presence there of the three alkaline secretions—the pancreatic juice, the bile, and the succus entericus. Weak solutions of soda, even in absence of any mechanical action, readily emulsify fats which contain free fatty acids [Gad (5)]. Fats, on the other hand, which do not contain free acids, are not permanently broken up either by soda solutions or by the bile, although the pancreatic juice may effect their division. Free fatty acids are either already present in and pass directly from the stomach into the intestine, or they are set free from the soaps of the bile by the acid gastric juice, or are liberated from the neutral fats by the rapid saponification produced by the pancreatic ferment. An emulsion of the fat therefore results in the intestine when the reaction there is almost neutral or faintly acid. This emulsion favours the action of the steapsin on account of the fine state of division of the fats present, and thus brings about the further emulsification and decomposition of the new supplies of fat from the stomach. The emulsification and decomposition of fat are processes which mutually assist each other. The bile aids in the digestion of fats in virtue of its solvent power for fatty acids, in particular for oleic acid [Rockwood, Pflüger]. It increases the power of the pancreatic juice in decomposing fats, although it is inactive itself; these two secretions combined decompose three times as much fat in a given time as is decomposed by the pancreatic juice alone [Nencki]. Glässner found that the power of the human pancreatic juice in splitting up the fat molecule was increased five times by the addition to it of bile and succus entericus (5). Complete breaking-up and saponification of fat are not, however, alone sufficient to ensure its absorption. When the bile is absent, these two processes may still be adequately carried out, as is shown by the complete decomposition of the fats which appear in the fæces in such a case, although they have not been utilized by the body [Röhmann, Fritz Müller (3)]. The bile, therefore, performs the other functions of making the intestinal villi moist and receptive for fat [Wistinghausen, Voit, Heidenhain (6)], and of stimulating the cells to an active absorption of the same.

The Form in which the Fats are absorbed.—During the whole process of digestion there is present in the small intestine, along with finely-divided neutral fat, quantities of free fatty acids, of soaps, and of glycerine. Munk (7) found 10 to 12 per cent. of fatty acids, together with 88 to 90 per cent. of neutral fat (the soaps were not estimated).

The form in which fat is taken up by the epithelial cells is still a matter of dispute. Many of the best-known works have long since agreed that it is absorbed in an undecomposed condition, as triglycerides in a very fine state of division, and that the hydrolysis which undoubtedly occurs in the intestine only extends to a small quantity of fat necessary for the complete emulsification of the rest. Other investigators of equal repute believe in a complete splitting up of the fat molecule, and hold that fats can only pass through the epithelial walls of the intestine as soaps or products soluble in water. The old dispute of fifty years ago in regard to fat absorption has been recently vigorously renewed. Pflüger gives his authority for the complete solution of the fats, and Henriques and Hansen, Cohnstein, and others support his views; Munk, Friedenthal, Hofbauer, Exner, etc., oppose them (8).

Of particular importance in connection with this question are the experiments of Friedenthal and his conclusions. Aqueous "soap solutions" are not, according to him, real solutions, but are colloidal, and do not diffuse. Besides this, as others have shown, solubility in water is not the same as protoplasmic solubility. Milk-sugar is taken up neither by the blood-corpuscles nor by plant-cells, although oleic acid, which is insoluble in water, is readily absorbed by these structures, and is also taken up by the epithelial cells of the intestine. It is probably the presence of lecithin which causes the absorption of oleic acid. "The absorption of fat does not depend on a diffusion of the soaps, but rather the reverse. The soaps must be decomposed in order to be absorbed as fatty acids" (8).

The Synthesis of the Fats in the Intestinal Wall.—One point is certain: whether the fats pass through the intestinal wall, completely or only partially decomposed, no "decomposed" fat exists immediately after its passage, neutral fat only being present. The partial or complete splitting up of the fats in the lumen of the small intestine is immediately counteracted by a synthesis from the decomposition products within the wall of the intestine. This interesting fact was discovered in the feeding of animals on substances which contained soaps or free fatty acids instead of glycerides. These substances were taken up by the intestine just as readily as were neutral fats.

Radziejewski found that, of 60 grammes of soap, as much as 95 per cent. was absorbed by a dog, and Munk observed that an animal fed on 100 grammes of the fatty acids from mutton absorbed about 88 per cent. of the same (in comparison with 90 per cent. of an equal quantity of neutral fat) (9).

Munk and Rosenstein were able to identify free fatty acids in the chyle excreted by human beings fed with the same fatty acids (they used the easily recognised and well-defined erucic acid for their experiments). Of the greatest importance, however, is the proof brought forward by Munk, and since confirmed by von Walther and Frank, that the free fatty acids supplied are no longer to be found in the chyle as such or as soaps, but are present there largely as neutral fats. According to Munk and Rosenstein, the quantity of the neutral fat in the chyle is at least ten, and usually twenty to forty, times as great as that of the fatty acids, whereas the soaps in the lymph show no increase in quantity above that which is present in a condition of hunger. The glycerine necessary for this synthesis has been supplied by the body (probably from dextrose?).

The region in which this synthesis takes place lies between the surface of the intestine and the central lacteal of the villi, for the smallest lymphatic vessels have been shown to carry neutral fat. It is probably the epithelial cells themselves that effect the synthesis. Ewald succeeded in showing that the mucous membrane of the small intestine after removal formed considerable quantities of neutral fats during digestion with glycerine, soap, and soda; the presence of neutral fat was not only recognisable in the mucous membrane, but also in the free liquid—*i.e.*, that outside the tissue. Hamburger made the same discovery with the mucous membrane of the large intestine. It is astonishing, however, that neutral fat is to be found in considerable quantity in the intestinal cavity of animals fed on free fatty acids [Walther and Frank], and it would appear from this that glycerine is brought to the surface of the cell, and that here already a synthesis with the fatty acids occurs. Whether, as is accepted by Munk and others, the neutral fat, which is found in the intestinal lumen in such experiments, comes from the digestive juices, and not, therefore, from a synthesis occurring in the intestine, is doubtful in view of the relatively large quantity occurring there (9). The activity of the isolated intestinal mucosa with regard to the synthesis of fat from fatty acids and glycerin is now being worked out by O. Frank and A. Ritter (*Zeitschr. f. Biologie*, 47, 251, 1905).

B. Moore (9) has shown, by collecting the lacteal contents of a dog after a meal rich in fats, that the synthesis takes place in the intestinal mucosa. He also repeated the experiments of Ewald and of Hamburger, but found that neither the cell-free extracts nor the detached cells of the mucosa synthesized neutral fats. Moore concludes that the action of living cells is necessary for the synthesis, and that the latter is not brought about by enzemic action. The glycerine of the fat is not used for this synthesis, but is utilized for the production of the energy necessary for the process. The mucosal cells themselves are capable of supplying the needful amount of glycerine.

The Behaviour of Fats in the Large Intestine.

Although the quantity of neutral fat in the small intestine exceeds that of the "decomposed" fat occurring there [Munk, *vide supra*], nevertheless in the lower portions of the intestine the reverse conditions exist. Fr. Müller found 84 per cent. of saponified fat and 16 per cent. of neutral fat in the fat residues from the human fæces, and the exclusion of the bile from the intestinal tract did not affect these values appreciably [Röhmann, Fr. Müller, Munk (10)]. The large quantity of fat excreted in this latter case (to 85 per cent. in men [Müller]) is largely decomposed by the action of the pancreas (and of bacteria), and is present in the fæces chiefly as fatty acids, and in much smaller amount as soaps. By exclusion of the pancreatic juice, on the other hand, splitting-up of the fats only takes place to a slight extent [to 40 per cent., Müller], although other workers have found higher values [30 to 85 per cent., Abelmann; Deucher, 60 to 80 per cent. (10)].

The Channels for Fat Absorption.

The lacteals, on account of their outward appearance during fat absorption, were first recognised by Tiedemann and Gmelin as the channels for the absorption of fats (11).

Later, Zawilski and Munk and Rosenstein measured the quantity of fat flowing from the thoracic duct, and Zawilski estimated this for different periods of digestion in a number of dogs. The two Berlin scientists were enabled by means of a lymph fistula to collect from a girl the greater part of the chyle flowing through the thoracic duct, and thus found it possible to follow the whole course of digestion and absorption of fat on one and the same case. They recovered in the chyle collected during thirteen hours, 25 grammes (= 60 per cent. approximately) of the 41 grammes of lipanin administered, and in eleven hours, 55 per cent. of an equal quantity of mutton tallow. It is therefore certain that the greater part of the fat is carried by the lymphatic vessels, but whether all of it thus finds its way into the body is not yet certain. By feeding with fatty acids, at any rate, Walther and Frank recovered in the chyle only a small part of the materials actually absorbed. Frank also found that fatty acids were still taken up in considerable quantity when the lower end of the thoracic duct was ligatured, and Hamburger has confirmed this for neutral fat when the mesenteric lymphatic vessels are tied. From this it appears certain that, under abnormal conditions at least, when the normal absorption channels are closed, the bloodvessels are capable of carrying off fat from the intestine (11).

The greater part of the fat is absorbed in the small intestine. Honigmann found that only 0·4 per cent. and 2·7 per cent. of the 109 and 150 grammes of fat consumed appeared at an ileo-cæcal fistula. The large intestine also possesses the ability to complete an "after-digestion" of fat under certain circumstances, and its power of absorption of fats and soaps, according to Hamburger, is not less than that of the small intestine. The colon does not secrete a ferment capable of splitting up fats, and it has not yet been determined how far down the intestine the steapsin of the pancreas is still active. Hemmeter was not able to identify an unorganized ferment in the human fæces (11).

Duration of Fat Absorption.

The absorption of fat extends over a period of many hours, and with a maximum diet of fat more than twenty-three hours are necessary for its disappearance from the intestine [Zawilski]. In the cited experiments of Munk and Rosenstein on the human being, the discharge of lymph containing fat began in the second or third hour after a diet of 41 grammes of mutton tallow or of lipanin, increased during the fourth to the eighth hours, and was not quite complete after eleven and thirteen hours (11).

Decomposition of Fat by Bacteria.

Along with the decomposition of fat produced by ferments there also occurs a decomposition by bacteria in the digestive tract. The extent of the decomposition produced by the latter is not, however, known, for the decomposition products of fat produced by these micro-organisms are neither characteristic nor distinct in themselves, as are the bacterial cleavage products of protein. Too much importance must not be attached to this action of the bacteria. Nencki (12) has shown that the pancreas, which readily undergoes putrefaction, does not, with the aid of bacteria, split up more fat than is decomposed in presence of phenol without them. Friedrich Müller, in digesting human fæces for twenty-four hours with butter-fat or milk, also observed that the bacteria possessed but slight powers for the splitting up of fat (8 to 12 per cent.).

Many writers agree that under pathological conditions, when the pancreatic juice is cut off from the intestine, a continuous decomposition of fat may be produced by bacteria. This belief, however, is based rather upon theoretical considerations than upon experimental proof (12).

The *Bacillus coli communis* is able to split fat up to about 60 per cent. Extracts made from mucor-like moulds possess lipolytic qualities. Fatty acids are liberated from butter or cheese by the actions of several varieties of moulds.

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THE ABSORPTION AND SEPARATION OF THE MINERAL INGREDIENTS OF FOOD.

As has been already mentioned, inorganic substances are usually present in the food of man in such quantity as to meet the requirements of the body. "We receive them into the bargain." In the every-day life of a healthy individual no special care requires to be taken except in regard to the amount of water and sodium chloride ingested. According to Bunge (1), it is by a purely vegetable diet that an increased quantity of sodium chloride is demanded most of all. From the intestine the salts pass through the radicals of the portal system into the circulation. Only small quantities are carried forward with the chyle through the thoracic duct. K. B. Lehmann showed that potassium iodide and ammonium thiocyanate pass through the lacteals, and inorganic iron salts are transported in the chyle [Gaule, Abderhalden (1)]. The absorption of salts depends as little as that of organic food-stuffs on passive osmosis and the purely physical laws regarding the same. Streams directed in opposite directions are passing the same spot at the same time, one depositing salts and the digestive juices in the intestine, the other carrying salts into the body. The cells have their choice from the materials supplied, and many salts, such as the alkaline sulphates, are much more slowly absorbed than is sodium chloride [Röhmann (1)].

The relations between inorganic materials and the intestine are of a twofold nature, for the intestine forms not only the entrance-point for the salts into the system, but is also a place for their egress. Certain difficulties therefore underlie an estimation of the amount of the salts actually absorbed.

Chlorine and Sodium are chiefly consumed as sodium chloride, either as a constituent of food or as a palatable adjunct. Sodium is found in combination with carbonic acid, and in smaller quantity with vegetable acids. It is probable that it also exists in loose combination with proteins. Chlorine is also present in foods in combination with salts of potassium and of the alkaline earths. Sodium and chlorine are practically completely absorbed by the body, except in severe diarrhœa, when a considerable amount of $NaCl$ is excreted in the fæces [C. Schmidt, Röhmann, Stadelmann (2)]. In normal fæces only a few decigrammes of chlorine and sodium are to be found, so that not only the sodium chloride of the food, but also the greater part of the hydrochloric acid of the stomach, together with the sodium bicarbonate and the sodium chloride of the digestive secretions, is reabsorbed by the body. Analogous to this is the absorption of the sodium, which is introduced in combination with carbon dioxide or vegetable acids [Beckmann]. The power of the body to take up sodium salts is practically unlimited ; of 29 grammes of sodium given to a diabetic patient (a girl weighing 24 kilogrammes) in the form of sodium bicarbonate (120 grammes), only 0·13 gramme appeared in the fæces [Magnus-Levy (2)].

Potassium occurs in food, partly in combination with chlorine, and partly with carbon dioxide and phosphoric acid. The chief quantity is introduced with the vegetable foods. Potassium, like sodium, is very readily absorbed, as is shown by the rate with which it reappears in the urine [Forster (3)]. The total quantity of potassium salts taken into the stomach is not, however, absorbed, or at least a separation of these salts occurs in the intestine, for the fæces always contain potassium, as well during hunger [Fr. Müller (3)] as after flesh or vegetable nourishment. J. König (3) gives 0·35 per cent. as an average figure for the K_2O in the human fæces, which would represent 0·3 to 0·4 gramme potassium per diem,[1] and as the mean value for the potassium excreted daily in the urine is about 2 to 3·5 grammes, it is evident that the percentage excreted in the fæces is a high one.

The Alkaline Earths.—A portion of the calcium present both in animal and vegetable food exists in loose combination with certain albumin of acid character, but by far the greater part occurs in the inorganic state as salts of phosphoric and carbonic acids. Vegetable foods are generally richer in calcium than are flesh foods. Of the animal foods, eggs and milk are particularly rich in calcium, for the growing animal requires this element for the formation of bone; flesh, on the other hand, is low in its calcium content. Calcium salts also occur in drinking-water, but in fluctuating amount.

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[1] The quantity of potassium in the fæces is usually less.

The greater part of the calcium which enters the body passes into the fæces, although in varying proportions, according to the nature of the nourishment supplied. According to Bertram, (4) there is present—

	In the Urine.	*In the Fæces.*	
Of man	18 to 43 per cent.	60 to 82 per cent.	of the calcium consumed.
Of herbivora	4 to 5 „	94 to 110 „	
Of flesh-fed dogs ..	27 „	73 „	

The fate of the calcium is closely connected with that of the phosphoric acid. A considerable portion of the phosphoric acid appears in the fæces, and calcium occurs in union with it as well as with carbonic and the higher fatty acids.

A more or less considerable part of the calcium (from 0·1 to 0·5 gramme per diem) passes into the human urine, and has therefore been absorbed. The quantity of calcium excreted in the urine increases when calcium phosphate or carbonate is given; thus Soborow found in two cases that the amount of calcium excreted daily in the urine rose from 0·28, 0·31 and 0·22, 0·27 gramme to 0·7, 0·98 and 0·73, 0·87 gramme when he administered 8 and 10 grammes of chalk daily. The results obtained by other workers agree fairly closely with these figures, although the increase in calcium was not so great as in the experiments cited [Tereg and Arnold, Perl, on dogs; Riesell, E. Lehmann, Schetelig, J. Strauss, Herxheimer, on man (5)]. The insoluble inorganic calcium salts are dissolved in the stomach to a greater or less extent depending on the amount of hydrochloric acid present. They are only there absorbed, however, in the merest traces, the greatest absorption occurring in the upper parts of the small intestine [Raudnitz (6)]. There the dissolved calcium salts are transformed again into neutral or acid calcium carbonates and phosphates, and into the salts of fatty acids, the amount taken up by the body depending on the reaction of the intestine, on the quantity of carbonic acid and phosphoric acid, and upon the various fermentation acids present. The greater part of the calcium is excreted in the fæces, either because it has not been absorbed, or because after absorption and circulation in the tissues it has been eliminated via the intestine. Thus, during starvation a part of the calcium set free through the breaking down of the cell tissues appears in the fæces. Fr. Müller and Munk found in two such cases 69 and 32 milligrammes in the fæces, and 377 to 446 and 70 to 202 milligrammes in the urine (7).

Calcium salts when injected subcutaneously or intravenously pass out quickly and almost entirely through the intestine, the large intestine being chiefly selected, although minute quantities are excreted by the small intestine [E. Voit, C. Voit, Tereg and Forster, Bijgl, Rey, Rüdell (8)]. The intestine is therefore the primary organ for the excretion of calcium, the kidneys falling into second place.

On these grounds, therefore, it is futile to attempt to determine the amount of calcium absorption in the body, or the conditions of the normal body upon which this absorption depends. For the same reasons, the attempts to refer those diseases which depend on an imperfect deposition of calcium in the bones (rhachitis) to an imperfect absorption of calcium salts have failed completely [Rüdell (9)]. The general statement may, however, be made, that the greater the amount of acid constituents present in food or produced in the body (for example, from the sulphur of protein), then the greater is the amount of calcium appearing in the urine. With an increased acidity of the urine its power to dissolve calcium is also increased. This explains why so little calcium is to be found in the alkaline urine of herbivora, and so much more, comparatively, in that of carnivora. On the same grounds Bunge (10) explains the greater percentage of calcium in the urine from flesh diet compared with that from vegetable diet. More calcium appears in the urine after acid calcium phosphate than after the corresponding basic salt [Tereg and Arnold]. Hydrochloric and sulphuric acids increase the quantity of calcium eliminated by the kidneys [Schetelig, Gaehtgens, Rüdell], while the administration of alkalies somewhat diminishes it [Beckmann, Rüdell (10)]. In diabetic acidosis, and in other conditions in which greater quantities of organic acids are present in the tissues, the urinary calcium is considerably raised (to as much as 2·0), but falls when such cases are treated with large doses of sodium bicarbonate [Naunyn, Gerhardt and Schlesinger, Magnus-Levy (11)].

Magnesium.—Certain quantities of magnesium also appear in the fæces, although the amount of this substance excreted in the urine is much more considerable than that of calcium. According to Bertram (4), there is present—

	In the Urine.	*In the Fæces.*	
Of man	36 to 46 per cent.	53 to 61 per cent.	of the quantities consumed.[1]
Of herbivora	25 to 29 „	63 to 82 „	
Of dogs	65 „	35 „	

Fewer determinations of magnesium have been made than of calcium. Nevertheless, it has been shown conclusively that the former element is excreted from the body in the fæces during a period of fasting when the quantity appearing in the urine remains undiminished. In two cases of starvation reported by Fr. Müller and J. Munk (7) 6 to 10 milligrammes of magnesium appeared in the fæces, and ten to twenty times this amount in the urine.

Phosphoric Acid.—Phosphorus is always introduced into the body in the highest state of oxidation as phosphoric acid. It occurs largely as inorganic acid, but sometimes in organic combination, as in lecithin and in nucleo-proteides.

Organic Compounds of Phosphoric Acid.—Under the influence of the digestive secretions the organic compounds containing phosphoric acid are largely decomposed. This is true at least of test-tube experiments with these substances, and the changes produced in the intestinal tract may proceed analogously. Nevertheless, it appears that these changes do not result in the formation of inorganic phosphoric acid. For instance, lecithin treated in this way yields glycerin-phosphoric acid [Bokay (12)]. The phosphoric acid of the para-nuclein in casein, which was formerly described as insoluble, becomes largely soluble after short digestion, and dissolves completely under favourable conditions; it has been identified in the albumoses as fixed phosphoric acid [Salkowski and Hahn, Sebelien, Moraczewski]. The rapid splitting off of the phosphorus-holding nucleinic acid from the actual proteid group of the nucleo-proteid of the pancreas by peptic and tryptic digestion has been confirmed [Umber (12)]. The phosphoric acid of these organic compounds is undoubtedly largely absorbed. By feeding on lecithin the greater part of the "absorbed" phosphoric acid reappears in the urine [Politis (13)]. This is also shown by the experiments of Röhmann's students, for the phosphorus of casein, which in casein preparations is organically bound, but is excreted as phosphoric acid in the urine [Leipziger, Markuse, Zadik (13)]. From their figures one can calculate that at least 80 per cent. of the phosphorus, probably still more, was excreted in the urine, whereas 20 per cent. atmost appeared in the fæces. Similarly the experiments of Gumlich, Minkowski, and Loewi with pure nucleinic acid show that at least 60 per cent. of the phosphoric acid given in this form was absorbed (14).

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[1] These figures just as little represent the limits which occur as do those for calcium obtained by the same author.

Although it may be highly probable [Loewi] that the absorption of this phosphoric acid actually takes place in organic combination (as glycerin-phosphoric acid or some higher combination) (14), nevertheless this still remains to be proved. In the interior of the organism this union with organic substances is broken up in the processes of oxidation; the organic compounds of phosphorus appear only in small quantities in the urine. The small amounts of glycerin-phosphoric acid which Sotnischewsky found in urine were not increased by administration of lecithin [Politis, Oertel, Mandel and Oertel, Bergmann, Loewi (15)].

Inorganic Phosphoric Acid.—The organically-combined phosphoric acid in food falls quantitatively far short of the phosphoric acid of the salts. Human milk is the only exception, for in it, according to Siegfried and Stoklasa (16), almost all the phosphoric acid is present in organic form. Phosphates are absorbed in large quantities, but are only partially excreted in the urine, the rest being returned to the intestine. To what extent the latter process occurs depends on the supply of calcium in the food, and also on the quantities of acid and alkali introduced into the body or already present there.

This is shown by the proportions of phosphate in the urine, and in the fæces of the various animal species. Thus Bertram (4) found—

	Phosphoric Acid.	
	In the Urine.	*In the Fæces.*
Man	60 to 75 per cent.	27 to 39 per cent.
Dogs (pure meat diet) ..	92 „	8 „
Herbivora	0·4 to 1·7 „	81 to 101 „

The flesh food on which dogs excrete so little phosphoric acid in the fæces is also poor in calcium, and gives an acid ash. On such nourishment almost the entire quantity of phosphoric acid passes into the urine, so that the proportion of nitrogen to P_2O_5 in urine (8·1 : 1) is almost the same as in muscle (7·6 : 1) [C. Voit (17)]. The food of herbivora, on the other hand, is rich in calcium, and yields an alkaline ash.

When, therefore, the omnivorous human being and the herbivorous animals are fed on animal food alone, as they are during the period of lactation, almost the entire phosphoric acid content of the mother's milk, as well also as the calcium and magnesium, are absorbed [Blauberg]: By infants, 75·8 per cent. CaO; 76·7 per cent. MgO; 75·5 per cent. P_2O_5; by sucking calves, 97·3 per cent. CaO; 96·2 per cent. MgO; 98·9 per cent. P_2O_5 [Soxhlet (18)].

It appears, nevertheless, as is shown by Bertram's figures, that on the ordinary mixed diet most of the phosphoric acid excreted is to be found in the human urine, and only one-fifth to two-fifths in the fæces. The amount of P_2O_5 excreted is increased when the foods are of vegetable origin, and also when pure calcium carbonate is given. It is not possible, however, even on large doses of calcium, to reduce the amount of phosphoric acid occurring in the human urine to zero. In experiments by J. Strauss, after an intake of 18 to 26 grammes of calcium, the phosphoric acid in the urine fell from 2·84, 2·98 grammes to 1·71 grammes, and in a similar case of von Noorden's from 2·8 to 1·1 grammes (19).

The complete removal of the phosphoric acid from the urine of man and of dogs, as in the case of the herbivora,[1] cannot be effected. Acid sodium phosphate, when subcutaneously injected into sheep, is excreted in the fæces, and in dogs appears almost entirely in the urine, even when the intestine is overladen with calcium salts (Bergmann).

In dogs the separation of phosphoric acid by the kidneys is not affected by the addition of alkali if the food is not rich in calcium [Beckmann]; the phosphoric acid salts of the sodium and calcium of the food then pass out almost entirely via the kidneys [Markuse, Leipziger, Zadik]. It is only when an excess of calcium and alkali are together present in the food that the phosphoric acid usually excreted by the kidneys is conducted from and to the intestine. The phosphoric acid of the fæces comes, therefore, like the corresponding calcium and magnesium salts, partly from the unabsorbed residues of the food, and partly from the acid which, having taken its part in the process of metabolism, is returned to the intestine. The fæces during a period of fasting always contain considerable quantities of phosphoric acid along with the alkaline earths [in man 0·14 to 0·20 gramme per diem, Fr. Müller (20)].

Sulphur.—In contradistinction to phosphorus, sulphur is almost always taken up in an unoxidized form—namely, in stable union with the organic material of the protein molecule. It is seldom—and then more by chance than otherwise—absorbed as an inorganic salt from purely mineral sources.

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[1] Whether this is due to the diet or depends upon some unknown "influence of organization," is difficult to decide. The continued appearance of considerable quantities of P_2O_5 [1 to 2·0 grammes, Cramer, Rumpf and Schumm (19A)] in human urine, even after vegetable diet, does not contradict the possibility of completely removing this separation by suitable dietary. A part of the vegetable foods of man, the cereals, yield (just as does flesh) an acid ash, whereas the grasses and herbs of carnivora yield an alkaline ash. Cereals are equivalent to animal food in respect of the metabolism of the ash.

It is probable that the protein molecule undergoes a partial splitting off of sulphuretted hydrogen in the intestine, but this gas cannot, however, be identified in the upper portions of the intestine [Steinfeld, Abderhalden].

The fæces carry off only small quantities of sulphur compounds [in dogs corresponding to 3 to 10 per cent. of the sulphur consumed, C. Voit (21)], and then generally in the form of nucleo-proteides, taurin derivatives, and compounds of sulphuretted hydrogen, but rarely in the form of salts of sulphuric acid. Almost all the sulphur appears in the urine, partly oxidized, as combined or uncombined sulphuric acid, and to some extent as unoxidized or neutral sulphur.

Iron.—The question whether the mineral substances perform their functions in metabolism in organic combination, and to what extent their entrance into the body in this form is of importance for the nourishment of the system, or perhaps necessary for the same, has already been pointed out. It has been most thoroughly studied in connection with iron, and is of the highest importance in therapy. The conditions here are so far favourable in that the iron of the organism appears to react only in organic combination, and hardly occurs at all as a really mineral constituent of the body.

Inorganic compounds of iron are not present in the usual articles of diet, except to some extent in the iron-containing mineral waters; larger quantities are only prescribed by the practitioner. Organic iron occurs exclusively in certain foods—as, for example, the iron in hæmoglobin and its decomposition product hæmatin, and in particular that in the nucleo-albumins (the "hæmatogen" of egg-yolk, of milk, and of the eggs of the carp). Rich in iron, according to Bunge, are the yolk of egg, green vegetables, such as spinach, cabbage, fresh asparagus, wheat-bran, strawberries, cherries, etc.; remakarbly poor, on the other hand, are milk, rice, and finely-sifted wheat-meal.

As is well known, Bunge and Kobert (22) have thoroughly contradicted the assertion that the body is capable of absorbing iron from inorganic salts, except from concentrated doses, which corrode the intestine, and inhibit their employment for the formation of tissue hæmoglobin. Only the iron-containing nuclein substances of food appear to be absorbed from the intestine, and serve in the building up and renewing of the blood-pigments. That "organic" iron is absorbed is shown by the fact that iron is only present in this form in the ordinary diet; the experimental proof is to be found in the particular series of experiments conducted by Bunge's students, Socin, Häusermann, and Abderhalden, in which animals kept on food almost iron-free received measured quantities of certain organic iron preparations. Similarly Cloetta has shown that large quantities of iron (as much as 10 milligrammes Fe) disappear within a few hours from the ligatured intestine (22A).

Bunge attributes the power of the inorganic preparations of iron used so much in therapy to a "protective action," as the result of which the absorption of the iron-nuclein from the decomposition and separation products occurring in the intestine is ensured. This conception, however, which never found favour in the mind of the practitioner, has not been a lasting one, although the proof that inorganic iron compounds are really absorbed has been long awaited. It is futile to try to determine the absorption from the increase of iron in the urine [Hamburger, Gottlieb, Kumberg, and others (23A)].

It has been found that almost the entire quantity of iron given in the most varied forms appears again in the fæces, and that it is rare to meet with an increased excretion per the urine. The iron, which has circulated in the tissues, is eliminated almost entirely through the intestines, only minute traces being removed by the kidneys. These relations are best shown by the experiments performed on animals during stages of fasting. Bidder and Schmidt found only 1·4 to 1·7 milligrammes Fe in the daily urine obtained from fasting cats, whereas six to ten times this amount (about 10 milligrammes) was excreted in the fæces. Investigations on fasting dogs and on human beings yielded similar figures [Fr. Voit, Fr. Müller (24)]. Iron, when injected subcutaneously and intravenously, is selected and excreted by the mucous membrane of the intestine [Gottlieb and others (25)].

It was only when the transportation of the iron in the body was determined by microchemical reactions that the passage of inorganic iron from the intestine into the body was confirmed [Hochhaus and Quincke, etc. (26)]. By means of ammonium sulphide and the Prussian-blue reaction the passage into the epithelial cells of the intestine, and from there into the liver and the other organs, can be demonstrated. Further, Kunkel (26) succeeded in determining quantitatively an increase of iron in the liver of mice which had received ferric chloride in their food. Honigmann (27) has shown that the absorption of iron by the human being can, under certain conditions, be of considerable magnitude : from the intestine of a patient with an ileo-cæcal fistula 338 milligrammes of iron from 416 milligrammes given as citrate were absorbed within two days, and only 77·8 milligrammes (18·7 per cent.) of the original quantity appeared in the excrement from the small intestine. The question of absorption of inorganic iron is now decided in the affirmative, and not only for large quantities of the element, but also for quantities which do not produce corrosion of the mucous membrane of the intestine [Häusermann, Abderhalden (22A)].

In the alimentary tract iron undergoes certain changes. The inorganic salts are largely transformed into ferric chloride in the stomach, but soon, however, a large part of them lose their ordinary chemical reactions by entering into organic combinations (with protein or carbohydrates).

Organic iron is also appreciably altered ; in the epithelial cells of the duodenum it can be identified by means of ammonium sulphide, so that its combination with organic matter has been broken down [Abderhalden (28)].

The duodenum has been shown by all authors to be the chief centre for the absorption of iron, inorganic or organic [Abderhalden (28)]. The rest of the small intestine with its lacteals takes part, however, in the process of absorption. The lymph is undoubtedly partly responsible for the transport of iron into the body [Gaule, Abderhalden], but it is also carried by the blood-stream [Franz Müller (30)]. It is excreted from the body largely by the lower parts of the large intestine, through the colon and rectum [Glaeveke, Gottlieb, Hochhaus and Quincke, Abderhalden (31)], but in the thickened secretion from a ligatured coil of ileum Fr. Voit (32) found considerable quantities of iron (6 to 9 milligrammes Fe per diem to the square metre of surface). The bile does not take any appreciable part in the excretion of iron [Gottlieb, Fr. Voit (33)].

An excess of iron is deposited in particular in the liver and in the spleen, not only when it is given by mouth, but also when administered by other channels than that of the intestine [Gottlieb, Jacobi, Stendel, Zaleski, Kunkel (34)]. The same deposits accrue from that iron which is set free by an increased breaking down of the red blood-corpuscles in disease or in experimental poisoning [Quincke, Minkowski and Naunyn (35)]. If the iron which is present in the food is not sufficient to meet an increased demand on the part of the blood, the supply thus accumulated is immediately drawn upon and utilized. This is the case during the lactation period [Bunge (36)]. The young animals, receiving too little iron from the milk alone, use up more than four-fifths of their total supply in the liver. This iron comes from the mother animal, which gives up to its young during gestation large quantities of its reserve liver-iron in order to supply them with a store from which they can draw during the period when the iron supplied from without is insufficient [Abderhalden (36)]. Similarly in artificial anæmia the iron of the liver is used up to a small extent for the regeneration of the blood-elements [Kunkel, Cloetta (37)]. In normal conditions the liver prevents an artificially induced excess of iron by a gradual excretion via the intestine. Abderhalden (38) found that considerable quantities of iron were excreted from the large intestine of rats from six to fourteen days after the last doses of iron had been given in their food; and Gottlieb also found that it was not until after a period of nineteen days that the last traces of iron from 100 milligrammes subcutaneously injected into his animals appeared again in the excrement.

The Absolute Requirements of the Body in Iron.[1]—No clear conception can be formed concerning the absolute amount of iron required by the full-grown animal in order to cover the loss of iron from the system, which normally occurs when iron is not required for the formation of abnormal quantities of blood-elements. According to the experiments of Forster, as well also as from the results obtained by Socin (39), the technical details of whose methods are beyond objection, the body appears to normally require considerable quantities of iron. Forster found that large dogs lost 53 to 93 milligrammes of iron daily when kept on food containing little salt or iron, and similarly Socin's dog lost 34 milligrammes during eight days when 9 milligrammes of iron were consumed. In other experiments similar extensive losses in iron which cannot at present be accounted for were here and there observed. The minimal requirement of the body appears, however, to be less than this, and one is here guided by the quantity of iron excreted during a period of fasting. In cats it amounts to about 10·0 milligrammes [Bidder and Schmidt], and 5·8 to 9·9 milligrammes in dogs (determined in the fæces only [Fr. Voit]); it is remarkable, however, that the minimum is not higher in the case of human beings [Fr. Müller found 7 to 8 milligrammes iron in the daily excrement during fasting (40)]. Only the very lowest value for the amount of hæmoglobin which is broken down in the tissues can be calculated from these figures (2 grammes hæmoglobin), the actual daily decomposition being much greater, more hæmoglobin being decomposed for the formation of biliary pigment alone;[1] but it is possible, perhaps, that the iron set free is used up in the formation of new quantities of hæmoglobin. Upon a normal diet the metabolism of iron is probably greater than during hunger.

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[1] Although not really belonging here, this is now considered on account of its more easy representation.

The organism can exist for a short time under certain conditions on very small quantities of iron. Thus Hoesslin (41) found that on pure milk diet continued for three days the amount of iron excreted in the human fæces amounted to 9·9 to 11·5 milligrammes, and Stockmann and Greig, on a diet low in iron, found 3·7 to 11·4 milligrammes Fe, not much more than is separated from the body during fasting. On the ordinary diet the amount of iron in the fæces is higher (16 to 29 milligrammes) [Guillemonat (41)]. In very rare cases it happens that the growing animal (dog) finds the small quantity of iron in milk sufficient to meet the large requirements for the formation of normal quantities of blood-pigment [Häusermann (42)].

It has already been pointed out that only small quantities of iron are separated in the urine. For the human being this quantity has been successively estimated at 1 to 2 or 3 milligrammes iron [Gottlieb, Damaskin, and others (43)]. The higher value (8 milligrammes) of Jolle and Winkler stands alone, and may be due to the methods employed. Although the iron in the urine is not increased by the consumption of inorganic iron, it is stated that an increase is effected by supplying hæmatogen [Socin], hæmoglobin, and hæmatin [Busch]. It is not quite clear what this would signify, for the nature of the organic combination of iron in the urine is not yet sufficiently known. In many diseases—as, for example, in nephritis and in diseases of the blood, and in particular in diabetes mellitus—the quantity of iron excreted in the urine increases considerably, the cause thereof being at present undetermined (43).

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[1] *Stadelmann* estimated the bile pigment of the human bile at 0·5 gramme per diem. This would represent 10 to 12 grammes hæmoglobin, and about 50 milligrammes of iron.

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B.—EXTENT OF ABSORPTION AND THE FORMATION OF FÆCES.

A portion of the food taken in a mixed diet is passed in the motions. At first it was considered that these contained no more than the undigested residue of the food. But the work of Voit and his pupils has shown that the fæces are made up from three sources : (1) Residues of the intestinal secretions, which are also in part excretions, and so get rid of certain waste products (mainly mineral) from the body. Here, too, is included the débris of the dead epithelial cells cast off from the intestinal mucous membrane. (2) The remains of indigestible substances taken with the food. (3) Actual residues of the food that for one reason or another have escaped absorption.

1. Influence of the Intestinal Secretions on the Formation of Fæces.

The glandular cells of the stomach, intestine, liver, and pancreas all contribute to the formation of the fæces. This is shown by the fact that fæces continue to be passed even during starvation. Fr. Müller found that dogs weighing from 7 to 32 kilogrammes passed 0·66 to 5·8 grammes of dried substance in the daily fæces. The well-known professional fasting man, Cetti, voided 20 grammes of fæces a day (= 3·47 grammes dried substance), containing 0·3 gramme N and 1·3 grammes soluble in ether. Four other persons investigated by Fr. Müller excreted about as much as dogs of half their weight—2·0 to 5·9 grammes of dry substance, 0·11 to 0·45 gramme of N, and 0·25 to 0·48 gramme of ash in the daily motions.

L. Hermann was the first to examine the share taken by the intestinal wall in this excretion by means of doubly tied-off segments of intestine left in the body; the experiments were more carefully repeated by Fr. Voit later. After three weeks loops formed of 26 to 37 cm. of intestine in this way are found to contain as much as 13·7 to 20·7 grammes of fæcal substance (weight after drying). Fr. Voit holds that about nine-tenths of the fæces of dogs, whether fasting or on a meat diet, are derived from the secretions of the small intestine, and that the liver and pancreas do not contribute much thereto. It is undeniable, however, that certain biliary constituents, hydrobilirubin and derivatives of the bile-acids, can be recognised in such fæces.

It is not fully known in what form the N occurs in the fæces during either fasting or feeding. Nucleo-proteides are undeniably present, mucin and albumin are absent (Ury). For the rest, cholesterin, lecithin, neutral fats, fatty acids, soaps, and the mineral constituents of the body in general are all found in the motions during starvation. Some of these are excretions. Müller, J. Munk, and others (1) have proved that lime, magnesia, phosphoric acid, and iron are all of them excreted.

When food is taken, the nature and quantity of the digestive fluids secreted is augmented according to the quantity and the quality of the food, so, too, is the unabsorbed residue of these fluids. Investigating the case of a man on a non-nitrogenous and also inadequate diet, Rieder found the daily fæcal N 0·54 to 0·87 gramme,[1] values about 0·5 gramme greater than those found by Müller in starvation. This N can only come from the body, and illustrates the minimal value of the "secretion N" that is not reabsorbed. In researches where the food taken is nitrogenous it is impossible to discriminate the N derived from the food from that excreted by the intestine. Prausnitz, on the one hand, believes that the fæcal N comes mainly from the intestinal secretions, describing diets as "productive of more fæces or of less," instead of as "capable of incomplete or complete utilization." Ury, on the other hand, states that only 24 per cent. of the fæcal N (= 0·39 gramme N daily on a mixed diet) is derived from the intestinal juices. He proposes to distinguish between the two by stating that the N of the food-residues is insoluble in water, while that of the residue left from the secretions is soluble; but this contention is decidedly questionable (2).

When human beings or large dogs are fed upon diets that are highly nitrogenous, but are almost completely absorbed (meat and eggs, for example), values of 0·6 gramme to 1·2 grammes N are found, which are but little higher than those recorded by Rieder. The dried substance of the motions does not increase *pari passu* with the quantity of meat given. Thus Fr. Voit (2) found in the case of a dog:

	Grammes.				
Meat given (dried substance) ..	120	240	361	482	602
Fæces excreted (dried substance) ..	5	8	9	12	15

In experiments like these the dried residue and the N of the motions are both mainly derived from the residue left by the secretions; the food taken is absorbed almost entirely.

With other diets the facts are different. The daily fæcal N on a diet of 2 to 3 litres of milk is 1 to 1·5 grammes; on a mixed diet, 1 to 2 grammes; on a diet of black bread, pumpernickel, and vegetables, up to 4 grammes; the quantity of the motions is correspondingly enlarged. It is impossible to be sure whether any actual increase in the secretory work done by the intestine occurs on a mixed or a vegetable diet; it is, however, probable that the augmentation of the N excreted is due mainly to incomplete digestion of the food-stuffs. This view receives support from the fact, to quote one out of many, that, under the unfavourable conditions of a purely vegetarian diet, large amounts of carbohydrate also leave the body unused.

The Bacteria of the Fæces.—A number of authors, including Nothnagel (3), regard the bacteria as the main constituent of the fæces. In view of this idea the question as to the parts played by the intestinal juices and the residues of the food must be reconsidered. Most of the bacteria found in the motions were not ingested with the food. They are derived by the continually renewed pullulation of the intestinal flora, which may grow at the expense either of the nitrogenous secretions or of the food-stuffs. If Nothnagel's view is correct, the loss of N in the fæces would represent an actual injury done to the body by its parasitical inhabitants. Strassburger has submitted Nothnagel's statement to the test of analysis, and concludes that one-third of the dried residue of the fæces consists of bacteria, both during fasting and feeding. On the average 128 billion bacteria are passed per diem, containing 8 grammes of dried substance and 0·83 gramme of N; hence he believes that the bacteria and not the juices of the intestine give rise to most of the N which is not derived from the food. A. Klein gives a distinctly smaller share to the bacteria in the formation of the fæces. He also notes that only 1·1 per cent. of the total number passed are alive and still capable of propagation by culture (3).

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[1] Tigerstedt records similar figures. Renvall, giving much more carbohydrate than Rieder, found 1·50 and 1·52 grammes of N in the fæces, the diet containing 0·3 and 0·2 gramme of N. The Ca, P, and Mg were also more abundant in the fæces than in the food (2).

2. Influence of the Residues of the Food upon the Formation of Fæces.

The formation of the fæces depends largely upon the residues left by the food; these are much larger in herbivorous than in carnivorous animals. The quantity is not a matter of indifference, for it, to a large extent, expresses the work that must be done by the intestine. The volume has a purely mechanical action, stimulating the wall of the intestinal canal, increasing the peristalsis, and causing the intestinal contents to move onwards. Herbivorous animals, like the rabbit, die when fed on food which leaves no residue. Adult human beings are not so constructed that they can exist on diets which leave no residue, or even so little residue as pure milk does; it is only during their childhood that they can live on nothing but milk for long periods. On residue-free diets the peristalsis is sluggish, and this causes disturbances that are only subjective at first, but later cause objective upset of the digestion. The importance of these food residues is emphasized in the term "intestinal scourers" that has been given them. The carnivores, too, do not dispense with them willingly; just as they devour bones, so do the graminivorous birds swallow sand, feathers, and the like.

Vegetarians recommend that we should consume a large amount of food which leaves much residue. This is not so much the case with races like the Japanese, who prefer a vegetable diet, and live very largely upon rice which is poor in cellulose[1] and has been properly prepared for consumption by cooking, as with the full-blown vegetarian who lives mainly upon raw fruit, vegetables, and bread containing bran or even unground grain.[2] A diet of this type has an inordinate bulk. Thus a vegetarian examined by Rumpf and Schumm took 334 grammes of Graham bread,

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[1] Scheube (4) finds that the fæces, containing from 22 to 39 grammes of dried residue, are no greater than those of Europeans on mixed diets.

[2] The difference between these two dietaries is continually overlooked in the statements made about the metabolism "on vegetable diet." See also the comments on p. 41, note.

160 grammes of rice, and 140 grammes of oats (= at least to 1,000 grammes after cooking), together with 1,400 grammes of dates and apples. A diet such as this not only contains much less proteid (73·9 grammes = 11·8 grammes of N) than an ordinary one, but also saddles the intestine with extra work by reason of the great volume of indigestible material from which it has to extract what it can absorb (4).

The fæces are much increased on a diet such as this. One may take the dried fæcal residue as from 13 to 17 to 28 grammes on an animal diet, and as from 30 to 40 grammes on an ordinary mixed diet or a rice diet. But when the food is purely vegetable, and consists only of vegetables, black bread, and so forth, the quantity is doubled and trebled, rising to from 74 to 115 grammes (= 300 to 400 grammes when passed). The residuum of the food, and also particles of it that escaped comminution, leave the intestine, and with them go quite large amounts of proteid and carbohydrate which have not been properly brought into contact with the digestive juices because the food was not sufficiently broken up when swallowed. Simple elutriation of the fæces with water readily proves that this is so without any further analysis. The residue left on filtration may contain large amounts of undecomposed lentils, husks of peas, or asparagus-fibres, while such things as pickled cabbage, cherries, peas, mixed pickles, and so on, often reappear in the same condition as that in which they were swallowed.[1] A significant quantity of N appears in the fæces. Voit's (4) vegetarian passed 3·46 grammes of N (= 41 per cent. of the 8·4 grammes in the food) in the motions; Rumpf and Schumm's vegetarian passed 4·01 grammes (= 34 per cent. of the 11·8 grammes N taken). The weights of the fæces in these two cases were 333 grammes and 370 grammes. Such results are economically unsatisfactory, although they are always viewed with a peculiar relish by the subjects of such experiments. It should also be noted that habituation to a vegetarian diet brings with it no improvement in the so-called utilization of the food. A vegetarian of many years' standing could make no better use of his food than Voit's laboratory man, who took an identical diet for purposes of comparison (4).

Hence vegetable protein is not so fully made use of as animal protein. This is due solely to the different forms[2] in which they occur, the former being wrapped up in a stout covering of cellulose [Rubner (5, *b*)]. If this covering is removed, as was done by Konstantinidi (4) for wheat-gluten, 97·5 per cent. of the N may be absorbed, which is as good a result as animal proteid gives. Taking lentils whole, Strümpell absorbed 59·8 per cent. of their N; taking them ground up, the absorption rose to 81·8 per cent. Two researches of Rubner and Konstantinidi on the potato may be aptly quoted here. Rubner gave a diet of 3,077 grammes of peeled potatoes, taken with butter, vinegar, and oil, as a salad—*i.e.*, in large pieces. Konstantinidi gave only 1,700 grammes of potato cooked up and mashed with butter and salt (4). Examination of the fæces gave the following results :

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[1] Such "pickled" vegetables and fruits are useful for demonstrations on the treatment of constipation. As regards their capacity for being digested, the "nutritious" fungi are not a whit better than vegetables [Saltet (4)].

[2] Thus, elastin in tendons is hardly attacked at all in the digestive tract. But if finely-powdered elastin is given, at least 80 per cent. of as much as 67 grammes may be absorbed in man [Mann (4)]. For the digestion of cellulose, see the section on the Digestion of the Carbohydrates.

	Rubner.		*Konstantinidi.*	
Dried residue ..	93·8 grammes.		20·1 grammes.	
N	32·2 per cent.	of the input.	19·5 per cent.	of the input.
Fat	3·7 ,,		1·18 ,,	
Carbohydrate ..	7·6 ,,		0·74 ,,	

These figures are clear enough. Not only do the nitrogenous constituents of the vegetable diet, but also considerable proportions of the carbohydrates, escape from the intestine undigested. The unabsorbed fat, on the other hand, is hardly greater than it is on ordinary diets ; this is because the fat is not shut up in the residues of the food, but is readily accessible to the digestive fluids.

3. The Utilization of the Several Food-stuffs.

Carbohydrates.

As a rule the carbohydrates are fully absorbed from the human intestine, especially when they are consumed in the form of fine bread, puddings, rice, macaroni, etc. [Rubner (5, *a*)]. Reducing carbohydrates and dextrin are commonly absent from the fæces, while starch is usually present only in traces—1 or 2 grammes—*i.e.*, less than 1 per cent. of the input may be found on an ordinary mixed diet containing 200 to 400 grammes of carbohydrate. Here, too, one can easily recognise the harmful influences of improper preparation and of insufficient comminution of the food, or of indigestible constituents in it, that have been mentioned already.

The values that have been given for this loss of carbohydrate are very variable. Only a few observers have determined the quantity of starch and its derivatives in the fæces by direct analysis ; in most cases the nitrogenous constituents, the ether extract, and the ash have been subtracted from the dried fæcal residue, the remainder being then set down as " unutilized carbohydrate." But this remainder consists largely of cellulose and unknown substances, which are certainly not carbohydrates. Hence the actual loss of digestible carbohydrates on what is called a coarse diet is undoubtedly less than these figures make it appear to be. Rubner (5) found the loss 1·1 per cent. with bread made from the finest flour, 2·6 per cent. with coarse meal, 7·4 per cent. with wholemeal bread ; with the peasant's sour rye-bread[1] Meyer (5) found a loss of 10·9 per cent. In such cases fermentation plays an important part. The lower fatty acids are ingested in abnormal amount, and are more particularly formed in quantity in the lower part of the intestine ; they excite peristalsis, and hurry its contents through the intestinal canal.[1] Thus Rubner (5), giving 282 grammes of carbohydrate in the form of carrots, found 50 grammes (= 18 per cent.) in the motions. But the prosperous citizen, whose food is better prepared, will generally lose only 1 to 2 per cent. at most; the coarser dietary of country folk, containing much more carbohydrate, and the ration-bread of the soldier, etc., entail losses of 5 per cent. or often more [see Hultgren and Landergren (5)].

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[1] But on a mixed diet, strongly acid bread, given in large quantities, is used up just as well as weakly acid bread [Lehmann (5)]. It is not the acidity that prejudices utilization, but mainly the presence of cellular and cuticular hulls—the bran of crushed-meal breads [Rubner (5, *b*)].

Protein.

Practically speaking, the above-mentioned distinction between the fæcal N derived from the secretions or bacteria and that remaining unabsorbed from the food cannot be made. It is quite sufficient to contrast the intake of N in the food with the total output of N in the motions, setting down the latter simply as dead loss. This may all the more properly be done because the N leaving the body *per rectum* is not at all a negligible quantity, and must necessarily be subtracted from the N taken in the food.[2]

The proteins are well absorbed when given in such favourable forms as meat—whether raw, boiled, or roasted—eggs, the finer breads, and so forth, and give rise to 0·8 gramme to 1·2 grammes N—rarely more—in the stools [Rubner and others (6)]. With the average input of 90 to 100 grammes of protein this means a loss of from 5 per cent. to 7 per cent. of the N. The same is true of the good modern "prepared proteins," of plasmon, and the other preparations of the proteins of milk, and of the vegetable roborat, the utilization being 92 to 98 per cent. [Prausnitz, Neumann, Löwy and Pickardt]; with tropon the figures are not so good. With Witte's peptone, which was more used formerly, and somatose, which is still widely employed, the loss of N is much greater; it may reach 30 to 50 per cent., and even more when somatose is taken in such large amounts as 40 to 50 grammes [Zuntz, Neumann (6)]. The percentage of N lost by the inevitable excretion of nitrogenous secretions from the intestine appears to be greater when the diet contains little protein than when it contains unusually large amounts. Similarly a diet with little protein in it, and leaving only a small residue, makes little change in the above values; the finer qualities of bread and flour, butter, bacon, sugar, and soups form such a diet. But the loss of N grows greater if the food contains much matter that cannot be well absorbed.

On the ordinary mixed diet of a tolerably well-to-do household the daily loss of N should be from 1 to 2 grammes (= 6 to 10 per cent.). If vegetables, fruit, and wholemeal bread preponderate, the loss rises to 3 or 4 grammes (= 15, 20, and 30 per cent., or even more). There are statistics, mainly due to Rubner (6), that enable one to work out approximately how much of any given diet will be utilized. It must be noted that the N is often better made use of when a suitable mixed diet is given than it is in experiments made with the various food-stuffs given separately. This is particularly the case when cheese is added to a dietary. Thus Rubner (7) found that the addition of 200 grammes of cheese, containing 10 grammes of N, to a moderate diet of milk was so far from augmenting the absolute loss of N in the motions that it actually diminished it, the loss falling from 7 to 12 per cent. to 2·9 to 4·9 per cent. A similar instance is given by Malfatti (7).

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[1] If an average coarse meal is baked with sour dough, the acid taken is completely absorbed in the intestine, none of it appearing in the motions; Lehmann found that 100 grammes of very sour bread contained the equivalent of from 6 to 10 c.c. of normal acid (= 360 to 600 milligrammes acetic acid). The finely-ground material was soon almost entirely absorbed in the intestine [Lehmann (5)]. With sour bread made out of wholemeal, on the other hand, acetic acid appears in the fæces, together with large amounts of butyric acid—over 2·0 grammes a day [Rubner (5*b*)]—because the unabsorbed residue of the bread gives rise to much fermentation.

[2] This method of calculation is not correct for certain purposes, such as the investigation of the actual decomposition of proteins. For many reasons this question defies precise determination.

Individual variations must also be considered here. Thus Rosemann made a protracted and uncommonly complete series of observations, giving a very favourably compounded diet containing 75 per cent. of animal protein in the form of meat, and free from vegetables and alcohol. He found a daily average of 2·57 to 2·74 grammes N in the fæces (= 15 to 16 per cent.). So, too, Neumann's different investigations indicated a relatively poor absorption of N. Cow's milk is utilized very unequally by adults, and usually much less completely than it is by sucklings. Finally, von Noorden observed very various losses—from 4 to 10 per cent.—of N in a number of persons on the same simple diet; the losses might even be quite different in the same person at different times (7).

The nucleo-proteides and their derivatives of the food are, as a rule, well absorbed, but when consumed in large amounts a proportion reappears in the fæces. This is particularly the case with sweetbreads, those consisting of thymus tissue being but slightly absorbed. While the mono- and oxy-purins, xanthin and hypoxanthin, are entirely absorbed, the amino-purins, adenin and guanin, reappear almost entirely in the fæces (Walker Hall, A. Schittenhelm (4)].

The Fats.

The ether extract of the fæces is commonly set down as fat, but it always contains considerable amounts of lecithin and cholesterin, in addition to the neutral and the hydrolyzed fats. Even during starvation or the administration of foods freed from fat, the stools still contain fat excreted from the intestinal tract. Starving dogs weighing from 23 to 42·6 kilogrammes passed 0·18 gramme to 2·3 grammes of substances soluble in ether every day [Fr. Müller]. During a protracted fast Cetti excreted 1·3 grammes per diem; the fat in the fæces of his partner, Breithaupt, was only 0·57 gramme a day [Fr. Müller (8)]. Most of this fat comes from the intestine. Of the dried substance found by Fritz Voit in his tied-off loops of small intestine, one-third was soluble in ether, and consisted mainly of fatty acids and soaps.

If the diet is poor in fat but otherwise adequate, it may happen that the stools contain more fat than the food does. Malfatti (8) found 4·51 grammes of fat in the fæces when the diet, consisting of peas, contained only 4·06 grammes. Moderate amounts of easily digested fat were so well absorbed by the body that practically no increase in the fæcal fat could be observed after their addition to the diet. Thus Malfatti added 80 grammes of butter to the peas, and extracted from the fæces only 5·8 grammes, as compared with the 4·51 grammes given above. In the same way von Noorden (8) varied the amount of butter in an otherwise uniform diet, and found—

With 4·2 grammes of fat in the food, 2·4 grammes in the fæces, = 57·1 per cent. loss.
,, 42·2 ,, ,, ,, 4·6 ,, ,, ,, = 10·9 ,, ,,
,, 80·2 ,, ,, ,, 5·1 ,, ,, ,, = 6·36 ,, ,,

As the fat from the intestine varies, it may happen that more fat is excreted in the motions (*i.e.*, from 3·1 to 6·5 grammes) when the food is almost free from fat than when a great deal of butter is being taken. Thus on a mixture of starch and butter only 2·5 grammes out of 157·8 grammes reappeared in the stools [Rubner (8)]. Carnivorous animals (dogs) can absorb colossal quantities of fat—as much as 350 grammes [C. Voit (8)]. In man the upper limit is not so high, but quantities up to 200 grammes a day can be absorbed to within 2 to 3 per cent. [Rubner (9, *a*), Klemperer (9)] if given in suitable forms, such as butter, milk, dripping, or cheese. In exceptional cases human beings can absorb as much fat as the dog. Landergren (9) found that 326 grammes of oil (= 96 per cent.) could be absorbed out of 340 grammes given mixed up with a little alcohol and gum arabic, with a loss, therefore, of only 4 per cent.

The various animal and vegetable oils employed therapeutically, such as olive oil, oil of sesame, and cod-liver oil, are absorbed just as readily as butter or dripping (Stüve and others). Margarine, too, up to 150 grammes, is taken up only 1 to 2 per cent. less fully than butter [Hultgren and Landergren (9)].

In estimating the amount of fat lost in the fæces it is important to consider the total intake of fat. As much as 10 to 15 per cent. of the fat in the food may be lost under normal conditions if its input is low, as it usually is with the poorer classes, amounting to only 25 to 40 grammes a day. But such a loss would suggest a diseased condition if larger amounts of fat—80 to 100 grammes or more—were being given; under these circumstances not more than 4 to 6 per cent. should be lost. We have already seen (Rubner's experiment, p. 52) that when the food contains other indigestible ingredients—on a vegetable diet, for example—the utilization of the proteins and carbohydrates is much more impaired than that of the fats.

Incomplete absorption of fat only takes place when it is consumed in large lumps; Rubner (9, *b*), giving 96 grammes of bacon, together with meat and bread, found the loss 17·2 grammes (= 17·4 per cent.). The physical constitution of the fat and its melting-point are also of importance—the more tri-olein there is in it, the lower its melting-point; the more tri-palmitin and tri-stearin, the higher is its melting-point. Tri-olein is fluid at the temperature of the body; the other two melt at 62° and 51·5° C. respectively. If the melting-point of the fat lies much above the body temperature, it is not made sufficiently fluid in the intestine to be absorbed freely. Absorption is impaired if the melting-point is about 50° C., while fats melting at higher temperatures are practically not absorbed at all. The dependence of absorption upon the melting-point is exhibited in the following table, which is based upon the researches of J. Munk and Arnschink (10):

Author.	*Fat.*	*Melting-point.* °*C.*	*Per Cent. Loss in Fæces.*
1. A.	Stearin	60	91 to 86
2. A.	Stearin and almond oil	55	10·6
3. M.	Spermaceti	53	31
4. M.	Mutton fat	50 to 51	9·2
5. M.	Mutton fatty acids	56	13 to 20
6. A.	Mutton fat	49	7·4
7. M.	Lard	43	2·6
8. A.	Pork fat	34	2·8
9. A.	Goose fat	25	2·5
10. A.	Olive oil	fluid	2·3

Thus all fats melting below 43° C. are absorbed with equal readiness.

An interesting observation in this regard has been made by Fr. Müller. He found that the fats with low melting-points are completely absorbed from the intestine; those with higher melting-points only partially so. In his experiments, while the fatty acids of the milk given melted at 43° C., the fæcal fatty acids melting at 50° to 51° C. But when diarrhœa occurred, the fat in the fæces was considerably increased, and the difference in the two melting-points was no longer to be observed (10). (See also Munk's researches (10*c*) on dogs with biliary fistulæ.)

Substances soluble in ether that are not fats, such as lanolin, are of no use to the body, and are not absorbed [Munk (10, *b*)], even though their melting-points are relatively low. Connstein (10) finds the melting-point of lanolin 40° to 42° C. Paraffin, too, is not absorbed [Henriques and Hansen (10)].

The absorption of fats is influenced by the amount of free fatty acid they contain. Buchheim (11) ascribed the ready absorption of cod-liver oil to the large quantity of free acid in it, the acid facilitating the emulsifying, and consequently the absorption, of the oil. This idea underlies the recommendation of von Mering's lipanin, which is composed of olive oil containing 6 per cent. of free oleic acid, and has the advantages of improving both the taste and the utilization of cod-liver oil. But the intestine while healthy is able to hydrolyze neutral fats in suitable quantity; hence butter and similar forms of fat are absorbed just as well as these preparations; see also Zuntz (11). The intestine does not lose this power in a number of chronic diseases in which cod-liver oil is often exhibited. F. Blumenfeld found that the absorption of butter and of milk-fat was just as good here as it is in health, and that it was not improved by lipanin, and Hauser (11) concludes that the apparently good effects of lipanin seen in children are not due to improvement in the intestinal absorption, but depend upon the increase in the quantity of the fat taken when its taste is improved and the stomach is in better condition.

The apparent improvement in the digestion of fat brought about by alcohol may be similarly explained. Among the educated classes the consumption of large amounts of fat is much aided by alcohol taken either with or after the fat, and so far the alcohol has its uses. But the utilization of the fat is not improved thereby. Atwater and Benedict have published the most complete investigations upon the action of alcohol. The mean of their numerous experiments in which no alcohol was given shows that 94·7 per cent. of the fat in the diet was absorbed; when 72 grammes of alcohol were taken at the same time the absorption was 94·5 per cent. (12). Klemperer holds that brandy exerts no favourable influence until large quantities of fat are given. He gave his attendant large amounts of spirits, and found that he absorbed 95 to 97 per cent. of 262 grammes of fat in his food. But the absorption was just as good when little or no alcohol was being given. Landergren gave 340 grammes of fat, together with 17 grammes of alcohol and a little gum arabic; Rubner gave 240 grammes of butter; Atwater and Sherman's bicyclist took 300 grammes of fat and more in a number of experiments; in none of these cases did the loss in the fæces exceed 5 per cent. (12).

It has also been supposed that the absorption of fat was promoted by the addition of lime-water or calcium carbonate [Klemperer (13)]. J. Munk improved the absorption of rape-seed oil in a dog by giving $CaCO_3$, but here the conditions were quite abnormal. The dog weighed 13 kilogrammes, and was given the relatively enormous amount of 175 grammes of this indigestible fat, which set up diarrhœa, and caused the loss of much fat in the motions. The $CaCO_3$ stopped the diarrhœa, and so improved the absorption of the oil. Similar observations have been made with the diarrhœas of children and adults; no doubt the chalk combines with the acids resulting from the intestinal putrefaction, and lessens the stimulation of the intestine. If the bowel is acting normally, large doses of lime may impair the absorption of fat by combining with the fatty acid set free [Forster]. Von Noorden found (13) that while 80 grammes of fat were being given, the loss rose from 5·2 to 11·7 per cent. when 25 grammes of $CaCO_3$ were added to the diet.

Mineral Constituents.

The excretion of mineral substances is peculiar in that it takes place largely through the intestine. Hence their utilization, and particularly that of phosphorus and iron, is not a little obscure, and reference must be made to the section on the absorption of the mineral constituents.

The Influence of Various Conditions upon Absorption.

Ill-balanced Diet.

The complete or nearly complete withdrawal of carbohydrate from the food does not materially injure the powers of the intestine for its absorption even when it has been discontinued for some time. This is illustrated by Hirschfeld's (14) experiments upon healthy persons, and also by earlier observations on diabetic people. But if the protein is much cut down the body suffers considerably as time goes on. After dogs had been given much reduced amounts of protein for six or eight weeks their digestive powers were upset [Munk, Rosenheim (14)]; the upset became grave, and the animals died. The absorption of fat was the most impaired, up to 28 per cent. of it being excreted in the fæces. The fæcal N was doubled or trebled, and the absorption of the carbohydrates was disturbed the least. Numerous severe anatomical lesions were found in the intestinal tracts of these dogs; hence their impaired digestion of the food must be attributed to failure of the intestinal secretions.

But this injurious effect of a diet poor in proteid has not always been observed in animals [Jägerroos]. And in man the experiments of Chittenden, who gave diets poor in protein for months at a time, have been equally free from injurious effects. Although the dietaries contained surprisingly little protein—no more than 40 grammes a day in his own case—neither he nor the twenty-five subjects of his experiments suffered from either digestive disturbances or abnormal losses of N. They must have made good use of the fat and of the carbohydrates also, seeing that there was no increase in the residue left on drying the stools (14). Reference should here be made to the chapter on Protein Economy, and to the section on the Lower Limits of the Proteid Intake.

The Effect of Constipation.

If opium is given in order to delay the excretion of the fæces, the stools contain less water, but there is no diminution in the amount of dried residue, N, fat, or so-called carbohydrate they contain. But it is otherwise in the more natural "chronic" constipation. Here all the food, cellulose included, is made better use of, the fæcal losses sinking to 75 to 50 per cent. of that observed in normal digestion [Lohrisch (14A)].

The Influence of Bodily Work and of Repose upon the Absorption.

Many years ago Ranke (15) demonstrated that the digestive organs contained much more blood when they were in active operation than when at rest. This led to the conclusion that digestion must be influenced by violent muscular exertion, which diverts the blood into the muscles. The familiar fatigue of the digestion which incapacitates so many people, do what they will, cannot be taken as evidence on this point, because it generally occurs only soon after the heavy midday meal, and at a time when the work of digestion is not near its maximum.

The problem can be attacked experimentally in two ways only. Either the activity of the gastric secretions and peristalsis can be examined, or the utilization of the food in the intestine. The results of the gastric investigations are discordant, partly because they have been made in different ways. Different results, too, are given by the digestion of protein and of carbohydrate. Cohn made dogs run about rapidly immediately after they had been fed, and found that the motility and secretory activity of the stomach were both diminished. Salvioli could only find a retardation in the formation of acids ; the passage of the food into the intestine was accelerated. Examining horses, Tangl noticed that the production of HCl was lessened, and that the food left the stomach more slowly ; in consequence, the gastric digestion of the starch went on more rapidly.

Spirig examined men, using Salvioli's method ; he found that while work did not diminish the production of HCl, it did hurry its contents out of the stomach. But Forster and Streng (15) found no constant differences between the gastric digestion during work and that during repose. The fact is that any slight differences here in the gastric and intestinal digestion would tend to equalize one another in the course of twenty-four hours. Temporary delays and alterations such as these in the digestion and absorption of the food have no lasting effect upon its utilization. The widely various experiments made by Grandeau and Leclerc, Wolff, and S. Rosenberg (16), upon animals, show that the organic matter of the food is turned to just as good account during strenuous work at it is during complete and continuous repose. And the same thing holds good for man. Thus Krummacher (16) found 1·005 grammes of N, on an average, in the fæces passed during six days of rest ; the average of seven days, with six hours of hill-climbing in each, was 1·17 grammes. Zuntz and Schumberg (17) examined soldiers on the march with similar results. It may perhaps be otherwise when untrained men suddenly take to violent physical exercise, but even the most strenuous exertions do not impair the utilization of the food taken by persons who are in training. The greatest performance of physical work known to me is that done by three competitors in an American bicycle race lasting several days, who covered 400 to 600 kilometres in from eighteen to twenty hours each day. Their exhausting work left but few minutes for eating and fewer hours for sleep. Their daily allowance of food was 169 to 211 grammes of protein, 178 to 198 grammes of fat, and 509 to 580 grammes of carbohydrate ; it did not cover their expenditure of energy, but was fully 50 per cent. above the diet of a man doing a moderate amount of work. The fæces of these three cyclists contained 6·7, 9·4, and 6·7 per cent. of N, 6·3, 2·0, and 12·7 per cent. of fat, and 1·1 to 1·6 per cent. of carbohydrate. Thus 93·4 to 96·0 per cent. of the dried organic matter in their food was absorbed, and no more favourable result could possibly have been anticipated [Atwater and Sherman (17)].

LITERATURE.

Amongst the most important works upon the formation of fæces and upon the quantities of several contained substances are : Fr. Müller, 1A ; Hermann, 1 ; Rieder, 2 ; Prausnitz, 4 ; Rubner, 4. Newer publications are comprised in the Bulletins of the U.S.D.A. (Atwater and pupils). A complete list of references (including the almost inaccessible Russian papers) is appended to the papers of Atwater and Langworthy. "A Digest of Metabolism Experiments." Bull. 45. U.S.D.A. Consult also Schmidt and Strassburger. "Die Fæces des Menschen," Berlin, 1901-1903.

Foods.	*Food Intake, Grammes per Day.*					*Daily*	
						Dried.	
	Dried.	Nitrogen.	Fat.	Carbohydrate.	Ash.	Quantity in Gm.	Per Cent.
1,790 gm. cow's milk ..	224·0	10·59	53·7	—	—	15·9	7·1
2,039 gm. „ „ ..	239·0	11·30	57·4	—	—	10·3	4·3
2,438 gm. „ „ ..	315·0	15·4	95·1	—	17·8	24·8	7·8
2,050 gm. „ „ ..	264·9	12·9	79·7	—	15·0	22·3	8·4
3,075 gm. „ „ ..	397·3	19·4	119·9	—	22·4	40·6	10·2
4,100 gm. „ „ ..	529·7	25·8	160·0	—	29·9	50·0	9·4
2,200 gm. „ „ ..	264·0	11·06	69·1	—	16·94	21·5	8·1
3,000 gm. „ „ ..	360·0	15·03	94·2	—	23·2	23·2	6·1
3,000 gm. „ „ ..	350·6	13·28	111·8	119·8	23·1	31·4	8·9
884 gm. roasted meat ..	366·8	48·8	20·9	—	18·6	17·7	4·7
614 gm. meat, 450 gm. bread, 95·6 gm. lard	545·0	23·6	99·0	259·6	23·5	46·5	8·5
600 gm. meat, 450 gm. bread, 191·2 gm. lard ..	610·7	23·53	194·7	226·4	22·5	56·0	9·2
600 gm. meat, 450 gm. bread, 240 gm. butter ..	615·0	22·98	214·0	221·5	25·5	41·3	6·7
630 gm. rice, ox-marrow, salt, meat-soup	660·2	10·4	74·1	492·9	23·8	27·2	4·1
898 gm. bread from fine meal	615·3	10·20	6·69	528·8	12·39	24·8	4·1
882 gm. bread from medium meal	612·5	13·19	5·65	507·9	12·89	40·8	6·7
989 gm. bread from whole meal	617·1	12·45	12·65	504·5	18·54	75·7	12·3
Rich, mixed, easily-digested diet	—	—	—	—	—	—	—
Rest experiment without alcohol	Without Ash 537	18·3	69	354	—	—	—
Rest experiment with alcohol	507	18·5	47	273	—	—	—
Work without alcohol ..	674	17·3	130	436	—	—	—
Work with alcohol	631	17·1	121	331	—	—	—
Rich mixed food, difficult to digest (f. Swed. Marine) ..	786·5	24·6	54·1	551	27·8	105	13·4
1,802 gm. pure vegetable diet, different varieties	719·0	8·4	22·0	557·0	15·0	75·16	10·0
Milk (1 litre), minced meat, butter, white bread, egg ..	360·0	17·2	80·0	154·0	—	40·7	11·2
Rice, potatoes, white bread, cakes, butter, sugar, honey ..	—	6·92	122·0	470·0	—	25·5	—
Rice, sausage, beef-tea, salt, gherkins	—	7·3	33·54	325·5	—	15·0	—
Rice, meat, butter, extract, salt, gherkins	—	15·78	40·47	289·6	—	9·3	—
Meat, eggs, oil, butter, salad ..	—	21·5	218·0	—	—	22·7	—
500 gm. meat, 2 eggs, little white bread and butter, 200 gm. salad	—	20·55	64·05	38·3	—	21·2	—
Meat, eggs, sausage, bread, butter, cocoa, fruit	—	14·57	156·3	193·1	61·0	—	—
The same plus rice, sugar, cakes, butter	—	15·36	227·5	423·7	61·5	—	—

Loss in the Fæces.								*Remarks.*	*Author.*
Nitrogen.		Fat.		Carbohydrate.		Ash.			
Quantity in Gm.	Per Cent.	Quantity in Gm.	Per Cent.	Quantity in Gm.	Per Cent.	Quantity in Gm.	Per Cent.		
0·58	5·4	1·5	2·8	—	—	—	—	Girl, aged 12	Camerer (18).
0·38	3·4	1·6	2·8	—	—	—	—	„ „ 10	„
1·0	6·5	4·66	3·3	—	—	8·7	48·8	Healthy man	Rubner (19).
0·9	7·0	5·7	7·1	—	—	7·0	46·8		„
1·5	7·7	6·7	5·6	—	—	10·9	48·2		„
3·1	12·0	7·4	4·6	—	—	13·3	44·5		„
0·66	5·9	4·93	7·2	—	—	6·48	38·2	„	Fr. Müller (20).
0·77	4·8	6·57	6·9	—	—	9·12	39·4		„
1·14	8·6	5·65	5·1	0·0	0·0	8·66	37·08	Men	Prausnitz (21).
1·2	2·5	4·4	21·1	—	—	28·0	15·0	„	Rubner (22).
2·86	12·1	17·2	17·4	—	1·6	6·7	28·5	„	„ (23).
3·30	14·0	15·17	7·8	—	6·2	5·7	25·1	„	—
2·60	11·3	5·8	2·7	—	6·2	5·1	20·0	„	—
2·1	20·4	5·2	7·1	4·5	0·9	3·6	15·0	„	Rubner (24).
2·17	21·3	2·99	44·7	5·83	1·1	2·39	19·3	„	„
3·24	24·6	3·55	62·9	13·10	2·6	3·90	31·2	„	„ (25).
3·80	30·5	6·47	51·0	37·23	7·4	8·34	45·0	„	„
—	—	—	—	—	—	—	—	—	Atwater Benedict (26). Gruppe :
1·3	6·9	4·2	6·2	7·8	2·2	—	—	„	A-C 13 Tage.
1·2	6·6	3·4	7·4	7·1	2·6	—	—	„	10 „
1·4	7·9	5·6	4·3	8·7	2·0	—	—	„	D-F 16 „
1·1	6·0	4·2	3·5	5·9	1·8	—	—	„	10 „
5·4	21·9	12·5	23·1	47·2	8·6	11·6	41·6	„	Hultgren- u. Landergren (27)
3·46	41·0	6·69	30·0	17·08	3·0	8·37	57·0	Vegetarian	Voit (4)
1·27	9·0	3·4	5·2	0·0	0·0	—	—	Healthy girl	V. Noorden (13)
1·46	21·1	3·16	2·6	—	—	—	—	Student	Peschel (14) u. v. Noorden.
1·01	13·8	1·88	5·6	—	—	—	—	Doctor	Miura (28) u. v. Noorden.
0·72	4·6	1·38	3·4	—	—	—	—		
1·11	5·4	3·25	1·5	—	—	—	—	Student	Kayser (29) u. v. Noorden.
1·26	6·1	5·03	7·9	—	—	—	—	Doctor	Dapper (29) u. v. Noorden.
2·75	18·9	5·11	3·3	5·4	2·79	—	—	Student	Krug (29) u. v. Noorden.
2·57	16·7	6·4	2·8	5·7	1·35	—	—	—	„

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III

THE FATE OF THE FOODS INSIDE THE BODY

A.—THE FATE OF PROTEIN.

1. The Synthesis of Albumin in the Animal Body.

The Building Up, Metamorphosis, and Degradation of Albumin

YEARS ago the " purpose " of the splitting up of protein in the intestine was thought to be to make it soluble and capable of being absorbed. At the present time the " significance " of the decomposition is this: that it enables the albumin of the food to be changed into the albumin of the tissues. The two forms differ in both the number and the combination of their C-containing nuclei, so that the transition from the one to the other makes a more or less extensive preliminary decomposition inevitable. In earlier days, as at the present time, physiologists believed that the protein of the food was reconstituted into the body protein. Until a few years ago it was supposed that the synthesis was affected by the more complex aggregates, such as albumoses and peptones. But the recent work of Löwi, Cohnheim, and Kutscher and Seemann (1) shows that the products of a more advanced decomposition are, in point of fact, engaged here.

The problem of the synthesis of protein in the animal body resolves itself into a series of single questions. Most of these cannot be fully answered at present, but I shall endeavour to settle them as far as the present state of our knowledge permits. An examination of the possibilities that present themselves may perhaps be of service by suggesting experimental methods for their investigation.

We shall discuss the following points :

1. Can the protein of the body be built up from the protein in the food ?
2. Is such a normal synthesis inevitable under all circumstances ?
3. Within what limits does this synthesis of protein take place ?
    - (*a*) How far must the previous decomposition go ?
    - (*b*) What, theoretically, is the maximum yield ?
    - (*c*) How great is the yield actually realized in the body ?

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[1] To avoid interruption of the exegesis by the insertion of details, these have mostly been relegated to footnotes in this chapter.

Four more questions must be added here :

4. Where is the metamorphosis effected ?
5. Of what kind is the protein first synthesized ?
6. Does protein undergo metamorphosis in the body ?
7. Is protein degraded in the body ?

(1) Can a Synthesis of Protein take place ?

From a chemical point of view the synthesis of fat from its constituents is readily intelligible, and the conditions under which it takes place in the wall of the intestine are so favourable that its occurrence there can be directly and completely proven. Fat is brought into the body by the chyle, which flows slowly and contains but little that is soluble in ether. While fat is being absorbed the chyle contains ten or twenty times as much of it as it does during fasting—as much as 5 per cent. or more. Hence it is possible to obtain the fat which has been absorbed, free from admixture with other fats, in a brief space of time, and in quantities sufficient for analysis.

With the proteins it is otherwise. The great velocity of the blood on the one hand, and the small quantity of proteins absorbed in unit time on the other, make it impossible for us to trace the passage of such substances or to differentiate them from the great mass of the proteins contained in the blood.[1] At the present time *all conclusions as to the synthesis of protein in the animal body are indirect, being based in the last instance upon the determination of the protein balance-sheet.*

If an animal can be fed upon the decomposition products of proteins for several days[2] to the total exclusion of protein, and kept in nitrogenous equilibrium on such a diet, or even put protein on, then a synthesis of protein is proved. The fate of the greater part of the nitrogenous groups absorbed is indifferent under these circumstances, because some of them must have served to replace the body-protein, which never ceases to undergo decomposition. Some of the attempts to prove this synthesis by feeding with albumoses and with Witte's peptone have very nearly succeeded. But a number of the older investigators did not adopt all the precautions now regarded as essential. In other experiments the issues were confused by giving undecomposed protein (in foods like rice, etc.) at the same time. And the best of these investigations—namely, those of Ellinger, who used Witte's peptone, and Blum, who gave protalbumose[1] derived from casein—lasted for only two or three days (2). Anyhow, it appears that certain albumoses, either alone or together with peptone, are able to replace the protein of the food. True peptone given alone cannot do this. For one thing, it possesses purgative and other actions; for another, it does not any longer contain all of the C-containing nuclei necessary for the building up of protein; it contains no tyrosin, etc. In fact, to render the synthesis of albumin possible, it is necessary, or at any rate preferable, that all the products formed by the cleavage of the protein molecule should be present together in the food. This idea was outlined by O. Löwi (2), who fed a dog upon self-digested pancreas that had almost ceased to give the biuret reaction. In eleven days the dog put on 9·8 grammes of N, at least 5.5 grammes of which came from these decomposition products that no longer gave the biuret reaction. The significance of this research is further treated on p. 68. *Cf.* also, "Amino Acids and Metabolism," L. Barker, *B. M. J.*, 1906, vol. ii., p. 1093. This paper contains an exhaustive review of the literature to date.

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[1] With carbohydrate the conditions are somewhat better than this. If large quantities of grape-sugar are taken in the food, so much of it is absorbed in unit time that one can easily demonstrate a definite excess of sugar in the venous blood from the intestine, as compared with the smaller amount present in the blood of its arteries. Assuming that from 1 to 2 litres of blood pass through the vessels of the small intestine during digestion per minute (=100 litres per hour), the latter quantity may well take up 50 grammes of sugar, but hardly more than 10 or 15 grammes of albumin. Arterial blood contains but little sugar—0·1 per cent.—and the increase to 0·15 per cent. is readily demonstrated. But an increase of 2 grammes in the N of the blood (=0·002 per cent. in 100 litres), which already contains 3 per cent. N as protein, and 0·02 to 0·035 per cent. N in the form of non-protein, cannot be recognised.

[2] Nitrogenous equilibrium must be maintained for at least several days, otherwise it is not possible to exclude the temporary cloaking of any loss of protein by the retention of non-protein N in the body.

(2) Can a Synthesis of Protein be dispensed with at Times?

Taking the possibility that a synthesis of protein in the animal body may occur as proven, it remains to ask whether there are circumstances under which the body can do without it. Under the ordinary conditions of nutrition the synthesis might perhaps be but little employed.

Regarding the processes of digestion from a teleological point of view, there are many reasons for believing that the synthesis of protein finds wide application. Its necessity and constant occurrence have been generally regarded as obvious. But it is quite possible that the body might satisfy its demand for real protein by absorbing a portion of the protein of the food in an unchanged or only slightly changed condition, while it might oxidize the cleavage products of the latter as soon as they were absorbed, and without first reconstituting them into protein. Brücke, Fick, and to some extent Voit also (3), to mention no more, have expressed themselves in this or a similar sense.

The amount of protein actually needed by the organism is doubtless smaller than the quantity of protein decomposed while food is being taken, as calculated from the excretion of N. In man the actual need is perhaps no more than 20 to 25 grammes a day; such an assumption can, at any rate, be made while this view is being considered.[2] Thus one might imagine that out of 100 grammes of protein human beings absorb one quarter undecomposed and in the form of protein, the rest being split up, absorbed, and applied without reconstruction to the performance of work or the production of heat.

As a matter of fact the intestine is able to absorb protein held in

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[1] Fed with heteralbumose from fibrin, Blum's dog lost N.

[2] Sivèn's daily decomposition for seventeen days was at the rate of 4·5 grammes of N. His food contained 2·96 grammes of N, not quite 2 grammes being in the form of protein. and he excreted 1·5 gramme N (=about 10 grammes of protein). On the assumption that the amido-N of the food was not turned into protein before use, his actual protein decomposition was about=2·2 grammes. Landergren (3A) was able to reduce his decomposition of protein to almost the same low level.

solution without preliminary decomposition. This is proved by the experiments of Voit and Bauer, Heidenhain, and Friedländer (4) upon the absorption of muscle-juice, serum, and egg-albumin from tied-off segments of intestine, for the intestinal erepsin does not break down these forms of protein. And the passage of at least one variety of protein unchanged into the blood can be recognised under normal circumstances—this is in the case of raw white of egg. Ascoli was able to recognise it in the blood by means of the "biological reaction," and also showed that part of the albumin subsequently excreted in the urine was egg-albumin.[1] In earlier days it was commonly believed that the intestine was unable to absorb any protein unchanged, seeing that such absorption would introduce new varieties of protein into the circulation, which the body would be unable to decompose or utilize.[2] But in view of the investigations of Neumeister, and of Munk and Lewandowsky, and others, this objection can no longer be sustained.

At the present time it is impossible to say what proportion of these new varieties of protein, reaching the circulation either directly or after metamorphosis in the intestine, is worked up into tissue-protein by the body and consumed in the nitrogenous metabolism. It is undoubtedly the case that the body is able to convert one variety of albumin into another without the help of the intestine. Reference should be made to Section 6 below.

The more nearly the structure of a protein in the food corresponds to that of the proteins in the body, the more one is justified in assuming that it can be absorbed with little or no change. The greater the difference in structure between the two, the less is such an assumption justifiable. The latter is the case with herbivorous animals, and in human beings who select their food mainly or wholly from the vegetable kingdom such a synthesis of protein must be, to a certain extent, taken as inevitable.

(3) The Limits of the Synthesis of Protein.

(a) *How far must the Preliminary Decomposition go?*

It was formerly believed that the intestinal cleavage of protein stopped at the formation of peptones, and that the body-protein was reconstructed from these. Two facts supported this view—one, that peptone could be recognised in the intestine and not in the venous blood flowing from it; the other, that the intestine and no other tissue[1] is able to bring about the disappearance of peptone [Salvioli, Neumeister, Hofmeister (6)]. More recently the formation of protein, not from peptone, but from "crystalloid products of cleavage," has been assumed to occur. Kutscher and Seemann have found large amounts of these in the small intestine. Cohnheim has demonstrated[2] that the disappearance of the peptone reaction in the intestinal wall is not due, as Hofmeister states, to the reconstruction of protein from peptone, but that is a consequence of the further decomposition of the peptone there. Löwi, however, has, more than anyone else, made it at any rate seem probable that protein can be synthesized from the biuret-free cleavage products derived from the pancreas, as has been described above. His statements were traversed by Lesser, but on insufficient grounds; they have been confirmed in their essentials by Henderson, and also by the ample experimental work of Henriques and Hansen (7).

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[1] It is also not improbable that the serum-albumin secreted in the pancreatic and intestinal juices is reabsorbed unchanged, because it is tolerably resistant to the action of trypsin (Oppenheimer, Glässner (5A)]. Too much importance has been attached to the "biological" reaction for the recognition of unchanged proteins, owing to the ease with which it is applied. Its significance must be regarded as doubtful now that it has been shown that the reaction can sometimes be given by the products of protein cleavage.

[2] The earlier investigators found that when varieties of protein not occurring in the body were injected into the circulation, they mainly reappeared in the urine. The proportion between the quantity injected and that thus excreted was not measured. After this, Neumeister and Munk proved that even when vegetable albumin was employed, only a small portion of it was excreted by the kidneys, and that the more slowly the injection was made, the smaller this portion became. Since then this result has been frequently confirmed (Lilienfeld, Oppenheimer). How far the tissue-albumin can be economized by egg-albumin injected into the veins has not been settled; according to Sollmann and Brown (5), but little economy seems to be effected.

The authors mentioned above speak of the building up of protein from "crystalloid foundation stones." But certain limitations must be imposed here, because modern usage[3] understands by this term the simpler molecular nuclei of the final decomposition products. But pancreas digested till the biuret reaction is no longer given still contains highly complex polypeptides (see peptone and polypeptide), as E. Fischer (8) showed was the case with the tryptic digestion of a whole series of other proteins. Abderhalden and Rona (9) further demonstrated that mice lived longer when fed upon the products of the decomposition of casein by acid, which consist solely of the simpler nuclei of the protein molecule, than when they were given the products of the cleavage of casein by trypsin, which consist largely of peptides.[4] In any event, the opportunities for the synthesis are greater in the latter case. But even if the organism does possess the power of building up protein broken down by acid into the tissue-protein again, one is not therefore driven to conclude that it decomposes food-protein to such an extent under the conditions of normal nutrition. Large quantities of amino-acids and so forth have been found in the intestine, yet this does not prove that every particle of protein is broken down into these simple complexes here any more than the quantitative hydrolysis of fats in the intestine is to be inferred from the presence of fatty acids and soaps in it.

Theoretically, it might be supposed that the smaller and larger molecular complexes common to the protein in the food and the protein of the tissues would not have to be split off from the former before entering into the structure of the latter. Were Nature ordered by such purely chemical possibilities, vegetable feeders would be worse off than carnivores so far as the digestion of albumin is concerned, and the carnivore would probably fare best by confining his attentions to his own species and becoming a cannibal. In any case, it is of interest to remark how even herbivorous animals devour their own flesh and blood—still-born fœtuses and the after-birth—when occasion offers, and that the higher animals, birds, and mammals are bred up upon animal protein similar to their own for a period during their early days.

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[1] Of all the organs examined, excluding the intestine, only the rabbit's liver was found to possess this power; the dog's liver was not able to cause peptone to disappear.

[2] But only for the intestine of octopods.

[3] Di- and polypeptides have not yet been obtained in crystals. But as their crystallization, and also that of the peptones, will some day be effected, it is better to let the above expression for the final decomposition products drop.

[4] Abderhalden and Rona's experiments were not arranged like Löwi's, dealing with the duration of life, and not the working out of a protein balance-sheet. Hence they cannot be directly employed for the criticism of Löwi's results.

Do equal quantities of ferments acting for equal lengths of time upon vegetable and animal protein break them down with different strengths? And do they break down the different varieties of these two kinds to different extents? Extensive special researches have been made, but these questions cannot be answered in the affirmative at present, though some of the results obtained do speak in favour of such an answer. Even though test-tube experiments should fail here, yet the animal tissues might succeed in decomposing with different degrees of completeness the protein consumed, varying the amount of ferment secreted according to the variety of protein ingested. Such a thing is at least well within the bounds of possibility, for Pawlow's brilliant experiments have taught us that the regulation of the quantity and composition of the digestive juices is extraordinarily delicate.

(b) *What is Theoretically the Greatest Possible Yield of Tissue Protein out of the Protein in the Food?*

The question can be answered by a hypothesis that is at present quite unproven. If the organism is not able to convert one amino-acid into another, or at least into another containing more C-atoms, or to supply protein nuclei that are lacking, either out of the constituents of the protein itself or the tissue-protein, it is obvious that *a given quantity of protein in the food cannot yield an equal amount of body-protein.*[1] To put a case, supposing that—

	I. Leucin and Lysin.	*II. Tyrosin and Phenylalanin.*	*III. Diamino Bodies.*	
(A) 100 grammes body-protein contain	x	y	z	molecules.
(B) 100 ,, food-protein ,,	x (0·8)	y (1·0)	z (1·1)	,,
Then 100 grammes B = {80 grammes A	= x (0·8)	y (0·8)	z (0·8)	,,
+ residue	= x (0·0)	y (0·2)	z (0·3)	,,

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[1] This is perhaps just one of the reasons why it is invariably impossible to bring an animal into N-equilibrium by giving it only the amount of albumin that is decomposed in the body during protein starvation. Such attempts fail, whether the protein is given to the previously starved animal alone and at the rate of its protein metabolism during fasting, or whether the animal is first fed upon N-free food, and then given protein too at the same rate. But in this experiment one must not compare the nitrogenous metabolism during fasting with that which occurs when a scanty allowance of protein is added to a full carbohydrate diet. A second reason for this important fact is perhaps this: the different nuclei or nuclear complexes are not absorbed simultaneously, so that they are not always at hand in the proportions necessary for the reconstitution of protein. Possibly some of the "foundation-stones" are ill adapted for keeping, and undergo decomposition prematurely. It would hardly be possible to consider loss of protein through bacterial depredation as a third cause in the carnivora.

The decomposition of the N-containing chains, which are of importance in the synthesis of protein, very possibly begins with the separation of NH_3 even in the intestinal wall. Salaskin (10) examined the gastric and the intestinal mucous membranes, and also the venous blood from the intestine of a dog while it was digesting its food. Although

Thus no more than 80 grammes of body protein could be formed from 100 grammes of protein in the food, and a certain residue, 0·2 y + 0·32 molecules of II. and III., would disappear for lack of opportunity to take part in the synthesis.[1] This example could be readily put in the shape of a formula, but I forbear to do this because the data are so uncertain.

The scheme given above does not reckon with the possibility that closely-connected nuclei might be derived one from the other. Thus lysin might arise from leucin, phenylalanin, from tyrosin, and glycocoll might result from the breaking down of alanin, leucin, asparaginic acid, etc. But it appears quite unlikely, so far as our present knowledge goes, that the animal body can build up tyrosin out of the aliphatic amido-acids or synthesize leucin, etc., out of glycocoll.

Hence the composition of gelatin is very different from that of the tissue-proteins, and this is probably one[1] of the reasons that it can only partially take their place. Contrariwise, the organism must be able to get a relatively greater yield of true protein out of substances whose composition more nearly resembles that of its own protein; the less

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the blood circulated more rapidly during digestion, he found that it contained an increased percentage of NH_3, as did the mucous membranes, compared with the NH_3 found during fasting; the NH_3 in the arterial blood and in the other organs was not increased. But it is still too early in the day to draw such definite conclusions from increased percentages of NH_3 in the blood or in the wall of the intestine during digestion. The analytical technique is too uncertain, the physiological variations in the amount of NH_3 in different animals are too large, and the combined influences of the other factors at work here are too great and too complicated.

In connection with what has been said in the text above, it may not be out of place here to look more closely into the much-studied question of how far protein can be spared by the administration of asparagin and other amino-acids. Plants and bacteria can build up protein out of asparagin alone; it is certain, however, that animals cannot do so; but it is possible that asparagin and other similar bodies given in the diet might make good some deficiency of the protein in the food as regards the building up of body-protein, and in this way influence the putting-on of protein in a favourable sense (see the note on gelatin below). Zuntz (11) holds that asparagin given in the food may have a further favourable influence by diverting to itself the ravages of the bacteria in search of N, and so protecting the other nitrogenous complexes, but protection of this sort can only attain to measurable proportions in the herbivores, with their extensive intestinal putrefaction.

Everybody knows that the nitrogenous decomposition as determined by the urinary N is not identical in value with the decomposition of protein. But even when we disregard the non-protein N in the food, or subtract it from the total N in the urine, the remaining N does not by any means represent the protein decomposition. While N-equilibrium is maintained, only that quantity of N (multiplied by the approximative factor 6·25) which was actually built up again into protein after absorption corresponds to the actual protein decomposition. Absorption of protein and absolute protein gain are not identical; in some cases they may be so, in others they may not. See further on p. 71.

[1] Although the quantitative analyses are far from complete, it is certain that gelatin contains much glycocoll and very little leucin and aromatic amino-acids. That the variable composition of gelatin is no more than one of the reasons why it is so ill adapted for the building up of protein is shown by the following fact: A considerable quantity of it given in the food effects an economy of about 20 to 30 per cent. in the protein decomposition of starvation, but quantities three or four times as great only increase the economy to 40 per cent., instead of trebling or quadrupling it as might have been expected [Kirschmann (12)]. The loss of body-protein cannot be prevented by adding much non-nitrogenous food to even the largest gelatin diets. Rubner affords the only exception to this statement, and he brought a dog into N-equilibrium on a diet of gelatin and extract of meat. Hence a gelatin diet should be enriched by addition of the quantities of leucin, tyrosin, etc., in which it is lacking, in order to ascertain if N-equilibrium could be thus attained.

the difference between the two, the greater would the yield be. The protein of milk, for example, made up of casein albumin and so forth, must be very closely related, as regards the quantity of its chemical nuclei, to the general constitution of the protein varieties built up and laid down in the body of the suckling (*vide* Section 5).

(c) *How much Tissue-protein is actually produced from the Food-protein?*

An approximate answer can be given to this question in certain cases at any rate. From a practical point of view we may discriminate here between the absolute amount of the protein taken from the food by the body, and the biologico-chemically more important relative conversion of food- into body-protein. These are the absolute and the relative "yields" of protein.[1]

Truth to tell, we can only give the minimum values here because it is only in the case of some of the nitrogenous substances absorbed that we are able to be certain that they really are employed by the body for the synthesis of protein. Any nitrogenous food-stuff that serves to make good the inevitable daily loss of body-protein is undoubtedly converted into protein (= the "putting on" of protein). In adults the protein put on every day must be at least 20 to 30 grammes, as the nitrogenous decomposition, even under the most favourable circumstances, does not fall below 3 to 5 grammes. So the absolute minimum yield of protein from the food stands at 20 to 30 grammes. In cases where persons have been kept in nitrogenous equilibrium by a supply of 40 to 50 grammes of protein, the relative yield $= \frac{20 \text{ to } 30 \text{ grammes}}{40 \text{ to } 50 \text{ grammes}} =$ as much as 50 to 60 per cent. or more. A further quantity of N may also be reckoned as protein —namely, the amount retained[2] in the body during protracted feeding experiments. Lüthje (13) observed daily retentions of 10 or even 14 grammes of N (= 62 to 87 grammes) of protein for long periods at a stretch. Including the 20 to 30 grammes calculated above, this brings the putting on of protein up to 100 grammes a day, all derived from the food. Thus the absolute yield of protein may be very large; the relative yield, however, in the case just given was not large, for 300 grammes of protein were being given in the food. But a very high relative yield can be established in other cases with certainty; thus suckling animals store up a great deal of the N they take. The suckling calves investigated by Soxhlet put on an average[3] of 68 per cent. of the N in their food, and 72 per cent. of the N they absorbed. The figures for Michel's (14) suckling infants were 73 to 85 per cent. and 77 to 89 per cent. respectively.[1] From 90 per cent. to 95 per cent. of the nitrogenous "gain" occurs as protein put on; the rest is due to other substances. In addition to the formation of the protein put on, the protein of the milk has to make good the body-protein decomposed by the calf—a relatively small amount; further, not all the N in the milk is present in the form of protein. Hence one is quite justified in saying that the suckling is able to convert 90 per cent. of the protein in its food into the protein of its body.

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[1] The expression "gain of protein from the food" would also suit here; but I prefer to use "yield," because the words "protein gain" are often employed as the equivalent of the N or the protein put on by the body.

[2] As to whether the permanent retention of N does or does not imply the putting on of protein, see the section on The Decomposition of Protein.

[3] Certain calves gave higher figures; unfortunately, only the average figures are at my disposal.

This may be due to the fact that the proteins of the milk, particularly if it is the milk of animals of the same species, are peculiarly well adapted for reconstitution;[2] or else it may be the case that we are only able to identify the reconstitution in sucklings, and not in the adult: the matter remains unsettled. And it still remains an undecided question whether the adult organism builds up the bulk of the intestinal protein fission-products into protein once again in order to use them primarily for the protein economy and only secondarily for the production of heat, or whether it employs them directly and without previous reconstitution as nothing more than sources of energy. Fick, like Brücke, holds with the latter view mainly on the strength of observations made upon dogs. The dog can satisfy its need of protein with an amount that covers no more than 10 per cent. of its liberation of heat; on the other hand, it can defray its total expenditure of energy out of protein alone, decomposing ten times as much of it as in the previous case, a dog weighing 30 kilogrammes using up almost 400 grammes of protein. According to Brücke's views, it is possible that the dog while fed upon meat alone does not decompose any more actual protein in its body than it does during fasting, etc., in which case it would be living upon protein and amino-compounds just as under other conditions it lives upon protein together with carbohydrate and fat. Finally, Pflüger believes that all the protein of the food is transformed into tissue-protein even during overfeeding with meat.

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[1] Reckoned per kilogramme of body-weight, the protein put on is very large in amount. While suckling the calves put on 26·8 grammes of N (=167·5 grammes of protein a day); at 50 kilogrammes this equals over 3 grammes per kilogramme. Michel's infants put on 1·1 to 1·6 grammes of N a day (=7 to 10 grammes of protein); on the average 2·5 grammes of protein per kilogramme.

[2] The attempt has been made to settle the question by feeding experiments on adults. It was believed that more N was put on when casein was given than when equal amounts of other kinds of protein were taken. But the experiments did not lead to uniform conclusions, largely because they were not well adapted to answer this theoretical question. It cannot be properly attacked by giving moderate or large amounts of the different varieties of protein, and partially or completely changing them one for another, and then observing which variety leads to the greatest putting on of protein. The successful nutrition of even a single individual does not depend solely upon the nature of the protein he is consuming. A method should rather have been employed which has proved advantageous in the solution of certain other physiological questions. The demand for protein should first have been reduced to its minimum value by a diet rich in non-nitrogenous foods, and then the smallest quantities necessary for the maintenance of N-equilibrium should have been determined for each of the various kinds of albumin. If it were to be found under these conditions that the necessary quantity was smaller in the case of casein than with any other type of protein, there would be no doubt that casein was best adapted as regards "yield" to the putting on of protein. This exposition is mainly theoretical; the possible advantages of casein for nutrition are a more practical question. The two correspond only in part, and confirmation of the former could not be transferred directly to the latter. See further the section Food in the chapter on the Economy of Protein.

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Folin has recently advanced the view that protein catabolism may be divided into exogenous and endogenous; the latter is small, constant, and comprises the tissue metabolism, being represented in the urine by creatinine, sulphur, possibly by a small amount of uric acid, ethereal sulphates, and urea; the former varies with the food, and appears in the urine as urea and inorganic sulphates. The urea thus chiefly represents the excess quantity of ingested nitrogen which is broken down during digestion, and then after absorption is not built up into tissue-protein, but at once excreted as urea and inorganic sulphates. He argues that 118 grammes of protein in standard diets is excessive, and should be to a large extent replaced by carbohydrates.

(4, 5) Where is the Metamorphosis effected? Of what Kind is the Protein first synthesized?

Is it Neutral, Blood, or Tissue Protein?

According to the earlier views the protein is built up out of peptone, and this synthesis takes place in the wall of the intestine, since no other tissue in the body has the power of causing peptone to vanish [Neumeister, Hofmeister]. But now that Cohnheim has proved that the molecules of peptone vanish, not because they are built up, but because they are broken down,[1] the site of the synthesis of albumin has again become uncertain. The mind still bethinks itself of the intestinal wall here, for that is also the seat of the synthesis of fat; grape-sugar, on the other hand, passes through it unchanged, not being demonstrable as glycogen in any solid tissue until it is found as such in the liver. Kutscher found a leucin compound, first recognisable after acid hydrolysis, in the filtrate from extract of the intestinal wall freed from albumin, albumose, and peptone by precipitation with phosphotungstic acid. He believes that this fact argues for at any rate the beginning of a synthetic process in the wall of the intestine. But it is quite possible that this masked leucin had been absorbed as a di- or polypeptide in just the same form as that in which it was found in the intestinal mucous membrane (6).

If a complete synthesis of protein does take place in the intestinal wall, it must be a neutral protein that is formed, probably one of those found in the blood. One can hardly suppose that the intestine synthesizes and delivers just the particular variety of protein that is wanting in obedience to the reflex demands of the separate organs. It has been observed that the serum-albumin is diminished much more than the serum-globulin during protracted fasting [Burkhardt, Wallerstein, Lewinski, Githens (17)]. This has been interpreted to mean that the serum-albumin is the "neutral" protein first reconstructed from the food. But it is obvious that this is not a necessary inference.

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[1] Hofmeister's pupils, Embden and Knoop, made an unsuccessful attempt to go further than Cohnheim, and show that there was an increase in the amount of coagulable N-compounds in the mucous membrane of the intestine while loaded with peptone. This increase was proved by Glässner for the mucous membrane of the stomach during digestion, but Salaskin has established some important objections to his view.

In opposition to the view just given one must entertain the possibility, discussed by O. Löwi (18), that protein is built up from the fragments of the food-protein molecule, not in the wall of the intestine, but in the various organs of the body. If this were so the blood would carry molecular complexes of the lower orders[1] from the intestine to the organs so as to cover directly their local necessities. These complexes would be built up into the protein of the organs *in situ* without having to pass through the preliminary stage of conversion into neutral protein. But such a supposition as this is by no means indispensable, for, as the following section will show, the organism is certainly able to convert even specific varieties of the protein of the organs into other kinds, and therefore would be able to build up organ-protein out of neutral protein.

(6) The Metamorphosis of Protein in the Body.

A metamorphosis of actual tissue-protein in the body can only be recognised for certain in starving animals in cases where an absolute increase takes place in the size or quantity of an organ, or in a variety of protein at the expense of a different variety of protein otherwise constituted. It may also be recognised when a species of protein is excreted that is not to be found in the body.

The best example of a protein metamorphosis of this sort is the growth of the sexual organs at the expense of the vanishing lateral muscles[2] seen in the fasting salmon [Miescher (20)]. Protein is metamorphosed by the milch-cow—she does not immediately cease to form casein when her food is withheld; so it is, too, by fasting persons who continue to excrete mucin during catarrh of their mucous membranes. Persons who excrete from 36 to 70 grammes of Bence Jones's or Noel Paton's protein a day in the urine continue to excrete these substances during starvation, although in diminished quantity [N. Paton, Magnus-Levy (20A)]. The synthesis of nucleo-proteides in maturing hens' and insects' eggs, neither of which contain any purin bases, and other instances, may be here referred to [Kossel, Tischomiroff (20)]. Seeing that the organism is thus able to interchange the proteins of the tissues, which are distinctly though slightly differentiated, one can well believe that it has the power to build up the specific kinds of protein out of the neutral protein of the blood. The intestine would then hand on just half-manufactured stuff made up out of the raw materials it received, but the organs would perfect the work and produce the finished article.

There is no need to enlarge upon the fact that a hydrolytic cleavage must necessarily precede every transformation of protein inside the body. This decomposition will go on in the same way as it does in the protein of the nourishment in the intestine, though it will generally not proceed so far. In the metamorphosis of protein, decomposition would only be excluded supposing that it consisted exclusively in the annexing of new groups—that is to say, in a growth of the molecule.

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[1] Or at least compounds that no longer give the biuret reaction, for Neumeister and other observers fail to find such in the blood. At any rate, they are not present there in increased quantity after food has been taken [Embden and Knoop (19)].

[2] The growth of the hind-legs of the fasting tadpole while the tail shrinks away (Pflüger) does not imply any metamorphosis, seeing that muscle-protein is here giving rise to muscle-protein. In the same way the growth of the fœtus at the expense of the fasting mother does not necessitate the preliminary decomposition of the maternal protein, which only has to be converted into the similar protein of the embryo.

(7) The Degradation of Protein.

The "living molecule" of protein in protoplasm, as the bearer of life, the instigator and agent of all chemical changes, has to enter into a temporary alliance with the lifeless combustible substances, the dispensers of energy, in order to initiate and carry through their oxidation, thus transferring to itself as living force their potential energy.[1] Thus its composition must vary at different moments according to whether it has just annexed such combustible substances in order to oxidize them, or has just given them off again after combustion. But the differentiation will affect the side-chains rather than the "functional nucleus."[2]

If at any given moment there is an insufficient supply of the non-nitrogenous chains which dispense energy, the protein molecules may perhaps form some, for the time being, out of their own constituents, or else give off nitrogenous side-chains in their stead. Restitution must be made forthwith, however, if the protein molecule is not to suffer impairment of structure or function.

It has been suggested that under certain circumstances the glucose arising from protein might be excreted in the urine, whilst a portion of the nitrogen appertaining to it might remain in the body, at any rate for some little time. In such cases it has been thought that a protein, impoverished in glucose, or at any rate differently constituted, would be found in the body [Umber (21)]. In this way the remarkable disproportion often found between the sugar and the nitrogen of the urine would be explained. But this quite leaves out of sight the fact that such a process could only yield an excess of sugar (above the proportion of 2·3 or 4·4) for a short time, and that after a certain period all the protein present in the body would have given off its sugar, and therefore would have undergone degradation in its totality. Besides, arithmetical considerations apart, such a supposition takes too little into account the most simple chemical aspects of the matter. In such comparatively simple products as the polycyclic and heterocyclic compounds of organic chemistry the replacement of a CH_3 group in a side-chain by CH_2OH or COOH entirely changes the character of the compound. The introduction of a second nucleus, such as benzene or pyrrol, renders the original substance almost unrecognisable. The chemical properties of the protein molecule are extremely delicate in nature; is it to be expected that the molecule will retain its multifarious capacities for chemical reaction unchanged after losing numerous atoms of C, H, and O, united in the form of $C_6H_{12}O_6$? Umber (21) believed he had found proof of such degradation of protein; he found in the bodies of starving animals a different $\frac{C}{N}$ quotient and a different proportion in the various amino-acids to those which obtained in normal animals (Kraus found the same in animals poisoned with phloridzin). But the methods they employed cannot afford sufficient proof, as they do not admit a quantitative determination of the protein "foundation stones." Abderhalden and his fellow-workers have raised analytical objections to Umber's and Kraus's experiments, and oppose the inferences they draw from them with well-sustained theoretical considerations; the results they obtained in their own investigations also contradict Kraus's and Umber's (21) assumptions.

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[1] Consider the mechanical activity of the muscles, produced certainly at the expense of the carbohydrates, etc., but which is set in action by the molecules of the protein.

[2] According to Ehrlich, and also to Pflüger, the living properties of the protein are invested in the functional nucleus. Kossel's "protein nucleus," which he takes to be a complex resembling the protamines, is the smallest structure which characterizes protein as such, and is common to all kinds of protein. These "nuclei" have nothing to do with Hofmeister's nuclei, the "foundation stones" of the protein molecules.

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Iron in the Synthesis of Hæmoglobin.

The building up of the red colouring matter of the blood, which therapeutically we are so often able to influence, is of especial interest, and therefore demands a more particular examination. All that we know of the process amounts only to this: that inorganic iron may be effectually introduced into hæmoglobin, in contradiction to the teaching of Bunge and Kobert (1). This is the only fact with which we can deal here; the synthesis of globin and hæmatin is at present entirely unknown. The usefulness of inorganic iron for the above-mentioned purpose was first fully proved by experimenting on animals with artificially produced anæmia. Young animals at the end of their period of suckling, when, as Bunge discovered, they had almost entirely used up the large amount of iron provided at their birth, are better for this purpose than fully-grown animals rendered anæmic by repeated bleedings. If these young animals are subsequently given only milk, or some other nourishment which is poor in iron, it is easy to make them very anæmic either with or without any blood-letting, for their provision of iron is not sufficient to supply the particularly strong demand for the building up of blood-pigment which is occasioned by growth. If, however, inorganic iron is added to the diet of such animals, their percentage content of iron, as also their richness in hæmoglobin, far surpasses that of the other animals under observation to which no iron is given [Kunkel].[1] An increase takes place not only in the percentage of hæmoglobin in the circulating blood, but also in the absolute amount of hæmoglobin contained in the whole body [Hösslin, Cloetta, Franz Müller, Hausermann, Abderhalden (2)]. This new formation of blood-pigment by the use of inorganic iron is clearly proved—at least, in the case of dogs and rats—by the fact that all the investigations of the above-named authors yield results which agree. On the other hand, it must be observed that, where the effects of inorganic and also of organic preparations of iron, such as hæmatin, hæmoglobin, and ferratin, were compared with those of the nucleo-proteides containing iron in ordinary food, the latter were found to be superior almost without exception. Thus Franz Müller observed that by the addition of ferric tartrate to milk the amount of hæmoglobin in a dog rose to 6·8 grammes per kilogramme of its body-weight, whilst another dog, without iron, had only 5·7 grammes of hæmoglobin. But the third dog, which was given nucleo-proteides in normal quantities in ordinary food, had 8·1 grammes hæmoglobin. Eger, Hausermann, and Abderhalden obtained the same results with different animals (2).

On the other hand, no difference was observed in the effects produced by either inorganic iron or organic iron, so long as it was not in the form of nucleo-proteides. Cloetta (3) added ferratin to the diet of his first group of animals, all of which were being kept on a diet poor in iron; to the second group he gave lactate of iron, and to the third group no iron at all. Whilst the third group became extraordinarily anæmic, the animals of the two other groups yielded equal amounts of hæmoglobin. Only as regards the iron in the liver was there any difference; the animals with ferratin had amassed a greater store of iron in the liver than those receiving ferric lactate.

		1. *With Ferratin.*	2. *With Iron Tartrate.*	3. *Without Iron.*
Hæmoglobin in blood	at commencement,	100 per cent.	100 per cent.	100 per cent.
	after 4 weeks,	94 to 96 ,,	94 to 97 ,,	51 to 81 ,,
	,, 7 ,,	91 ,, 95 ,,	92 ,, 95 ,,	31 ,, 67 ,,
	,, 9 ,,	90 ,, 98 ,,	87 ,, 95 ,,	28 ,, 45 ,,
	,, 12 ,,	93 ,, 99 ,,	94 ,, 99 ,,	24 ,, 35 ,,
Iron in blood	,, 12 ,,	40·5 mg.	41·7 mg.	16·3 to 21 mg.
Iron in liver	,, 12 ,,	23·4 ,,	10·4 ,,	1·4 ,,

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[1] Of the animals observed, those given iron had in their blood 0·035 per cent. of oxide of iron, as against 0·020 per cent. in those which had no iron; and in the liver 0·032 per cent., as against 0·004 per cent.

All these experiments were carried out on animals whose food was poor in iron. The results had to be carefully substantiated before the influence of inorganic iron on the formation of blood under normal nutrition could be investigated. Here, too, the giving of iron chloride or iron lactate, etc., distinctly quickens and improves the formation of blood, carrying it beyond the average found in animals with normal diet [Eger, Abderhalden (4)]. Thus iron is clearly seen to exercise a "formative stimulus" on the organs which make the blood [von Noorden, Abderhalden, Franz Müller], a stimulus which also influences other organs. The growth of young animals can be much hastened by administering inorganic iron for a few weeks. Hæmatin does not possess the same formative power [Abderhalden].

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2. The Decomposition of Protein in Animal Tissues.

Cleavage and Combustion.

As far as the decomposition of protein in the body can be explained at present almost everything depends upon this question: Does this decomposition proceed to the formation of atomic complexes the same as, or similar to, those formed by ferments? It must be determined whether oxidation first sets in after the simple chemical nucleus, which is considered to be the "foundation stone" of protein, has been set free from the great molecular complex, or whether combustion is already initiated in the undivided complex. In the latter case it either might or must happen that the resulting molecular complexes would be different from those formed by hydrolytic cleavage.

So much at least is certain: that a large number of protein radicals either unchanged or at any rate in such a form as to leave no doubt as to their origin, reappear, both in sickness and in health, in the excretions and the secretions. Glycocoll is a regular constituent both of the urine and of the bile. Taurin can be clearly traced back to the cystin of protein [Friedmann, von Bergmann, Wohlgemuth (1)]. Cystin is also frequently found in the urine in its own form. Arginin is found as such[1] in the spleen [Gulewitsch and Jochelsohn (2)]. Penta- and tetramethylene diamine, which together with cystin appear occasionally in the urine during disturbances in the metabolism, are slightly changed derivatives of lysin and ornithin; the latter also occurs in birds under normal circumstances after they have been fed with benzoic acid. Leucin and tyrosin are given off in diseases of the liver, and together with them other amido-acids, etc.,[2] appear in the blood and urine [Abderhalden and Bergell, Neuberg and Richter, Ignatowski, Embden, Hall, and others]. The aromatic complex of tyrosin and of phenylalanin is found again in the urine in the shape of oxy-acids, just as is the case with homologues of benzoic acid. It is also, though slightly changed, still clearly recognisable in homogentisinic acid [Langstein and Falta (2)]. The cleavage of the purin nucleus already formed out of the nucleo-proteides, and its transformation into uric acid must also be borne in mind.

The regular or occasional appearance of most of the protein nuclei known so far in the intermediary or final metabolism speaks strongly in favour of the assumption that the path of the decomposition of protein lies chiefly through such and similar products. The objections to this view raised by Pohl, Wiener, Löw, and other investigators are not so weighty as to necessitate its withdrawal. Also Neuberg and Löwy are quite doubtful as to whether the physiological decomposition of the protein substances leads to a thorough splitting into "crystalloid decomposition products." This is because their cystinuric patient, who did not burn up the leucin, tyrosin, etc., which were added to his diet, did not excrete them under normal circumstances, and therefore could not have been in the habit of forming them from the protein he decomposed. But this might also be accounted for by supposing that the tyrosin and other substances supplied did not push their way into the cells when decomposition was taking place; whereas if the tyrosin was produced by protein within the cell it might at once part with its NH_3 and then become oxidized. Also the fact that the body is able to change one kind of protein into another (see p. 74) points to a capacity in the organism for decomposing protein hydrolytically. There is no doubt that it does at least occasionally make use of this power; that it often does so seems probable, but so far it has not been determined whether this is the only path it can follow or not (2).

(1) The Forces that decompose Protein in the Animal Body.

Autodigestion, or Autolysis.

The forces which effect the cleavage of protein in the organism have of late years been recognised and investigated. In almost every organ there exist proteolytic ferments, as well as others which act upon carbohydrates and fat; the former decompose the protein of the organs removed from the circulation by forming the same products as are liberated by the operation of pepsin or trypsin. Salkowski (3) was the first to recognise this process of autodigestion, or autolysis. He investigated it systematically, and has laid great stress upon its wide and universal bearing.[1]

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[1] It is apparently not quite certain that it does not arise from autolysis, however.

[2] Lysin, asparaginic acid, and others.

Leucin, tyrosin, glycocoll, xanthin bases, and many other bodies are brought into existence by the self-decomposition of isolated portions cl muscle or liver, under aseptic conditions. From none of the organs investigated so far—the spleen, brain, intestines, etc.—are proteolytic ferments absent. Besides the products of autolysis already mentioned, there are the following : ammonia, cystin, pentamethylenediamine, lysin, arginin, tryptophan, asparaginic acid and glutaminic acid, histidin (thymin, uracil, various purin bases, sulphuretted hydrogen, succinic acid, pentoses, etc.) [Jacoby, Hedin and Rowland, Kutscher and Seemann, Kutscher, Müller, Levene, Reh, Vogel, Schmidt-Nielssen, Magnus-Levy, Simon, Salkowski, Neuberg and Milchner, and others (3)]. As intermediate products of the decomposition, Jacoby (4) discovered proteoses in small quantities in the liver, in larger quantities in the lungs; peptone, on the other hand, was not to be found.

The intracellular ferments at work in autolysis do not originate in the digestive canal. They are not identical with trypsin, though related to it in their effects. The liver ferment splits up the globulin thoroughly and with energy, whilst it leaves parts of the albumin untouched. The autolytic ferments also differ among themselves ; for instance, the liver ferment destroys proteoses with much more vigour than does that of the lungs [Jacoby (4)].

It seems natural enough to transfer these processes which take place in excised organs to parts of the body which have been deprived of their blood-supply [Jacoby, Müller], and also to living organs in which the natural relations have not been disturbed. It is, indeed, not possible to prove directly such autolysis in the living organs, because here the formation of the products of decomposition is immediately followed by their oxidation and their removal in the circulating blood ; there is, therefore, never so large an accumulation of them as our modern methods of experiment require. Autolysis in the living body has so far only been partially recognisable under pathological conditions—for instance, in the liver in cases of phosphorus-poisoning [Jacoby], where the marked increase in the post-mortem decomposition observed is probably begun or prepared for during life by autolysis. Langstein and Neubauer examined a puerperal uterus, and found in it a degree of autolysis far beyond the normal; thus autolysis certainly plays an important part in the physiological involution of this organ (4).

It is true there are some difficulties in transferring the processes of autolysis to the living organism. In autolysis proteoses are formed, although in small quantities. This is in apparent contradiction to the doctrine that the body is not able to split off proteoses and peptones. Whenever proteoses or peptones have been injected subcutaneously or into the veins they have appeared unchanged or little changed[2] in the urine, apparently quantitatively, or else, if the kidneys have been removed, they have appeared in the intestinal canal [Hofmeister]. The animal body is not able to work up peptone, no matter how small be the quantity [Matthes (5)]. Proteoses have never been seen to appear in the body or in the urine as the result of normal metabolism. Whenever they have been observed in the urine in larger quantities under natural conditions—for example, in pneumonia, etc.—either bacteria have been at work at the same time, or else the decomposition of dead matter, such as infiltration of the lungs, has been going on. In other cases—for instance, in ulceration of the intestine—the proteoses of the urine are to be traced directly to the intestine [Chvostek (5)]. According to Chvostek, the tissues have no power to decompose proteoses. But this only applies to proteoses introduced into the cells from outside, as in the experiments given above, but not to proteoses generated within the cells, as they are during autolysis. The former might possibly not be able to push their way into the cells, or at any rate not so far as to the place where cleavage is going on, whilst that which originated in the cells would straightway be further decomposed—either then and there, or in other cells—into products, such as amino-acids, which become oxidized[1] under all circumstances.

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[1] It is true that isolated products of autolysis had been occasionally found before, but Salkowski was the first to recognise fully the existence of the process.

[2] The primary proteoses as heteroproteoses (Neumeister).

Jacoby is of the opinion that possibly proteoses may be able to pass from an organ—the lungs, for instance—into the circulation, and may be decomposed elsewhere, perhaps through the ferments of the liver, by "heterolysis." There is no insuperable difficulty in Jacoby's theory, as the presence in the blood of bodies akin to proteose has again recently been noted [Embden and Knoop, Langstein, although contradicted by Abderhalden and Oppenheimer (5)].

Little is known of the processes going on in their "foundation stones" after the cleavage of the protein. Certainly, after their further elaboration a splitting off of the terminal groups of carbonic acid occurs. In the same way diamines are formed from lysin and ornithin, and cystin from taurin, and to a certain extent this CO_2 cleavage is fermentation pure and simple [Emerson (6)]. The body is further enabled to get rid of methyl groups—at least, of such as are united to nitrogen. Thus, for example, xanthin, caffein, and theobromin are deprived of their several methyl groups by their passage through the body [Albanese, Bondzynski, and Gottlieb]. On the other hand, the body is able to employ methyl groups synthetically [His, Hofmeister, Neuberg, and Salomon (6)].

A study of the rôle played by proteins in the general economy of nutrition has been recently made by S. B. Schryver (6).

In conjunction with Miss J. E. Lane-Claypon he has shown that the post-mortem changes in the protein of the liver produced by the autolytic enzyme can be divided into three stages: (1) A latent period or period of very small change, lasting generally about four hours; (2) a period of rapid degradation, lasting for six to eight hours; (3) a period of slow gradual change, which can be represented on a curve by approximately a straight line.

The changes were determined by incubating the tissue, finely minced, with ten times the weight of water at 37° C., and estimating the nitrogen in the filtrate after coagulating by heat, and the addition of trichloracetic acid.

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[1] Amido-acids introduced into the blood are, unlike proteoses, for the most part entirely oxidized [Stolte (5)].

It was also found that the rate of post-mortem change is more rapid in the liver of a fasting animal than in that of an animal killed during the full height of digestion.

From the last fact it was concluded that the stability of the protein of the tissue was the resultant of the chemical mass action of three sets of bodies—viz., the protein of the tissue, the metabolites, or bodies produced therefrom, and the autolytic enzyme or enzymes. It was assumed that the presence of large quantities of metabolites, or bodies produced therefrom, would inhibit the action of the autolytic enzyme on the tissues.

The investigation of the rate of autolysis in the presence of the products of tryptic digestion of casein (taken as a typical food-stuff) revealed the fact that the latter exerted a strong inhibitory influence on the former.

It was of importance, therefore, to determine whether the product of tryptic digestion could be obtained in larger quantities from the serum and tissues of animals in the full height of digestion than from fasting animals. It was shown that some of the older methods of technique for investigating this subject were liable to error, and a new method was devised with the object of avoiding the inaccuracies discovered. The tissues or serum were mixed with an equal weight of anhydrous sulphate of soda, the mixture finely powdered, and then coagulated with hot alcohol. The total nitrogen of the protein was determined, as well as the nitrogen of the coagulum, and the difference between the numbers obtained (called the "residual nitrogen," German *Reststickstoff*) was calculated. In the event of the product of tryptic digestion circulating in the serum, or being taken up intracellularly, the residual nitrogen should be greater in fed animals than in fasting animals; this was found, however, not to be the case. The ratio of the residual nitrogen to total nitrogen in the serum and small intestine was the same in fasting as in fed animals, and in the liver somewhat larger in the case of fasting animals, owing, no doubt, to autolysis taking place *in vivo*.

From these results it was concluded that the chemical stability of the liver was not the resultant of the mass action of the products of tryptic digestion, the protein of the tissue, and the autolytic enzyme.

It was found, however, that acids, especially lactic acid, greatly accelerated the rate of autolysis, whereas alkalis (including ammonia) greatly retarded this factor. In the presence of sufficient acid the latent period was entirely abolished.

Now Nencki, Pawlow, and Zalecki have shown that ammonia is a product of protein metabolism, is produced in relatively large quantities in the digestive tract, and carried thence by the portal vein and other channels to the other tissues of the body. There is a larger amount of ammonia in the portal blood and in the liver of fasting than of fed animals; there is, furthermore, a larger quantity of ammonia in the portal vein than in any other part of the vascular system. It is obvious, therefore, that the rate of autolysis is influenced, not by the products of tryptic digestion directly, but by the ammonia produced therefrom by the metabolic processes taking place in the alimentary tract.

A quantitative study of these facts showed that the amount of acid necessary to abolish the latent period of autolysis was of the same order and number as that necessary to neutralize the ammonia stored up in the liver.

The latent period lasts, therefore, whilst the tissue remains alkaline. This leads to the study of another factor—viz., the formation of acid within the cell. Magnus-Levy has shown that acids are produced during aseptic autolysis (amongst others lactic acid). Furthermore, both fats and carbohydrates produce on oxidation bodies of acidic nature. It matters not, for the purposes of the present argument, whether such acids are produced by oxidation of the tissues themselves or by the oxidation of the stored-up food materials (glycogen, fats, etc.). As soon as the amount of acid produced exceeds the amount necessary to neutralize the stored-up ammonia or other alkali autolysis sets in, and nitrogenous equilibrium ceases to be maintained. In order, therefore, to maintain nitrogenous equilibrium, nitrogenous food-stuffs must be ingested in such quantities and in such form[1] that the ammonia produced therefrom in the digestive tract is sufficient to maintain the intracellular alkalinity of the liver and probably other tissues.

It is probable, therefore, that more nitrogen is necessary than that required to replace the wear and tear of tissues, the so-called " endogenous nitrogen " of Folin.

In well-nourished animals there is always an excess of ammonia present which gradually disappears as the animal is deprived of food. A certain stage will then be reached when the production of acid exceeds the amount of ammonia available for neutralization; the autolytic enzyme then comes into play, liberates amino-acids, etc., which in their turn pass to the alimentary tract, and by means of the metabolic processes taking place then liberate ammonia, which again inhibits the production of nitrogenous degradation products. Degradation of tissue should proceed, therefore, at a definite uniform rate.

Agencies which inhibit oxidation lead to the accumulation of lactic acid or other organic acids in the tissues, which under healthy conditions are oxidized further into carbonic acid. By this means an increased nitrogenous output is produced, and equilibrium ceases to be maintained in certain cases, such as in phosphorus-poisoning, when an animal is insufficiently supplied with oxygen, and under other pathological conditions, which are discussed in some detail in the original paper.

Another point of interest is the large percentage of residual nitrogen in the small intestine. This is a constant, and is independent of the state of nutrition of an animal. On direct coagulation of the moist tissue by heat only a part of the bodies represented by this nitrogen is eliminated. The whole is eliminated after incubation with water for four hours. By means of the sulphate-of-soda method already described, however, the whole is eliminated. It has been assumed from these facts that the bodies represented by the residual nitrogen are in a state of loose chemical combination with the bioplasm, such as exists between an enzyme and its substrate (or perhaps between a toxin and antitoxin). In this state they undergo certain chemical changes like hydrolysis or oxidation, such as would take place through the action of an enzyme; the products of change would be eliminated and carried in the blood-stream to other parts of the organism. After chemical change and elimination they would be replaced by other side-chains, which would in their turn undergo the same kind of changes. The more rapid the blood-stream through the organ, the more rapid would these changes be. According to this conception, then, the passage of the products of tryptic digestion through the mucous membrane is analogous to a continuous chemical process. The bioplasm acts as an enzyme, or collection of enzymes, to specific points by which side-chains are anchored; it keeps, furthermore, always saturated with side-chains, as is shown by the fact that residual nitrogen is the same during digestion as during fast. This saturation is maintained by means of autolysis.

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[1] Possibly also specific groups from protein degradation are necessary.

This theory is analogous to that suggested by Verworn to account for the utilization of carbohydrates.

Wakeman has found that during autolysis in physiological and pathological conditions the hexon bases are diminished, and that arginin is especially affected. Levene points out that when self-digested pancreas, liver, and spleen are submitted to the action of mineral acids, the cleavage products are much diminished when compared with those obtained from fresh glands.

(2) The Splitting off of Ammonia.

Of special importance for the elaboration of protein is the fate of the nitrogen therein contained and its cleavage from the amino-acids, etc. This frequently occurs before the oxidation of the C-chains—with which it is united—has begun or has been completed. The N and the C of the protein molecules go their separate ways; the whole of the N of the protein may have left the organism at a time when its equivalent C is still partly retained [C. Voit and his pupils].

M. Gruber (7) examined every two hours the N excretion of a dog fed on an excessive amount of protein, and compared it with the CO_2 and heat formation observed in respiration experiments. The quotient $\frac{\text{Urinary N}}{\text{Pulmonary } CO_2}$ was in the first fourteen hours greater, in the last ten hours smaller, than was to be expected from the simultaneous excretions of the N and C of the protein. The safest proof for a very extensive cleavage of N from the C-chains lies in the formation of grape-sugar, etc., from protein.

The way in which the N decomposition takes place, thereby leaving a remainder free from N, has been ascertained—at any rate, for certain bodies. The formation of paroxyphenyl lactic acid [Blendermann] and homogentisinic acid from tyrosin and phenylalanin shows how the N-atom may leave the original complex, while the C-chain stays behind.

Langstein and Neuberg (7) saw alanin change into lactic acid ; ammonia was simply split off and replaced by hydroxyl.

$$\underset{\text{Alanin.}}{CH_3 . CHNH_2 . COOH} + H_2O = \underset{\text{Lactic acid.}}{CH_3 . CHOH . COOH} + NH_3.$$

Paul Mayer has proved the splitting off of NH_3 from diamidopropionic acid ; after its injection into animals he found glycerinic acid in the urine.

It may fairly be objected, in cases like Blendermann's investigations and others, where amido-acids were introduced into the food of rabbits, that the splitting off of NH_3 is to be attributed to the bacteria in the intestine. But this objection falls to the ground when the substance has been injected under the skin. The formation of homogentisinic acid, formerly attributed to bacteria, undoubtedly takes place inside the body [Langstein and Mayer].

Bacteria are able to separate NH_3 from the amido-acids, etc., without breaking down the rest of the molecule.[1] Probably the living organism of the higher animals has the same forces at its command. But the autolytic ferments are able to turn firmly combined N, like that of the amido-acids, into weaker combinations, and to convert it into NH_3 [Jacoby]. S. Lang has been able to establish the likelihood that the amido group can be thus removed from glycocoll, leucin, and tyrosin by autolysis in a number of organs. On the other hand, the amido-nitrogen of asparaginic and glutaminic acids, also of phenylalanin and of cystin, was proved by his experiments to be capable of offering some resistance.

The living organism, among other capacities, effects a separation of NH_3 from methyl- and ethylamin [Salkowsky, Schmiedeberg], and also from benzylamin ($C_6H_5CH_2NH_2$), which thereupon is converted into hippuric acid [Schmiedeberg (7)].

A cleavage of NH_3 also occurs during the transformation of adenin and guanin to hypoxanthin and xanthin.

It thus appears that the process of " disamidization " is one which is widely spread, and which follows immediately upon the cleavage of protein into its elements, and generally or often precedes the oxidation of the C-containing residue. The pathological excretion of much amido-acid possibly is due, as one can well imagine in the case of diabetic glycosuria, not so much to any primary loss of the power to oxidize as to the inability to decompose ; in this case, therefore, it is due to the loss of power to split off the NH_3.

(3). The Oxidization of the Hydrocarbons in Protein.

We now to a certain extent understand the forces in the body which make for the decomposition of protein, but the ways and means of the oxidation, in spite of countless ingenious experiments on animals and with the test-tube, are still almost beyond our ken [*cf.*, amongst others, Drechsel, Hofmeister, Pohl (8)]. The study of the oxydases [Jacoby (1)] has so far given no directly valuable results for the oxidative decomposition of protein. It has only been possible here and there to seize upon products of decomposition, and those solely among the aromatic and not the fatty substances, and from them to draw conclusions as to the steps of oxidation, for here the benzene nucleus in many cases protects the side-chains from entire combustion. The production of oxymandelic acid, of uroleucic acid, and of homogentisinic acid out of tyrosin shows us how the ammonia group may be detached alone in exchange for hydroxyl (Formula I.), or how, under other circumstances, complete oxidation of the α- and partial oxidation of the β-carbon atom may follow the gradual removal of the terminal carbonic acid group (Formula II.).

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[1] Reduction often takes place here—*e.g.*, the formation of succinic acid from asparagin.

$$\text{I.}\quad \underset{\text{Tyrosin.}}{C_6H_4OH\,.\,CH_2\,.\,CHNH_2\,.\,COOH} + H_2O = \underset{\text{Paroxyphenyl lactic acid.}}{C_6H_4OH\,.\,CH_2\,.\,CHOH\,.\,COOH} + NH_3.$$

$$\text{II.}\quad \underset{\text{Paroxyphenyl lactic acid.}}{C_6H_4OH\,.\,CH_2\,.\,CHOH\,.\,COOH} + 3O = \underset{\text{Mandelic acid.}}{C_6H_4OH\,.\,CHOH\,.\,COOH} + CO_2 + H_2O.$$

Fr. Knoop (8A) has established one important rule on the basis of earlier experiments. This is that when the normal saturated "aromatic-fatty" acids are oxidized they are first attached at the β position. Under these conditions the C-atoms do not come away singly, but chains of two C-atoms are generally detached.

How far this rule applies to the aliphatic series cannot yet be determined. The only analogy so far observed in the aliphatic series is the oxidation of butyric acid into β-oxybutyric acid[1] (see the chapter on the Acetone Bodies). The above rule, as Knoop says, explains the fact that in milk only fatty acids with a regular number of C-atoms are present. That lower fatty acids were derived from the higher would be well explained by β-oxidation and the separation of groups of two C-atoms.

It is easy to understand that taurin is produced by oxidation from cystin :

$$SH - CH_2 - CHNH_2 - COOH + 3O = SO_2\,.\,OH\,.\,CH_2 - CH_2NH_2 + CO_2.$$

Review of the Processes of Protein Decomposition.

According to our present knowledge of the decomposition of the protein molecule three processes must be recognised and distinguished :

1. *The Cleavage of the Whole Molecule.*—This often undoubtedly brings into existence the same lesser molecules found in the fermentative and acid decomposition of protein. It is still unknown whether the decomposition taking place in the organism also proceeds in other ways,

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[1] In a certain direction the oxidation of mannite into lævulose, and of sorbite into sorbose, by the sorbose bacterium [Bertrand] is analogous to this. It is not the alcoholic C-atom standing at the end, but the C-atom next to it, which becomes oxidized, just as in the aromatic acids it is the β C-atom, not the α-atom next to the carboxyl, which experiences the first attack of the oxidation (8A).

either partially or completely, and whether other "molecular fragments" result than those formed in the test-tube.

2. *Disamidization.*—Whether this always precedes the oxidation of the C-containing residue cannot at present be determined.

3. *Oxidation.*—So far as this takes place in the protein "foundation-stones" which have been robbed of their nitrogen—that is to say, therefore, in hydroxylized and otherwise substituted fatty acids, the problem of their oxidation is partly connected with that of the oxidation of fatty acids (fats), and also partly with that of the combustion of alcohol-aldehydes (carbohydrate) and the acids which proceed from them.

(4) The Formation of Carbohydrate from Protein.

Under ordinary circumstances the carbon compounds left after the nitrogen has split off from the protein undergo complete combustion. But under many conditions they are transformed in the body in quite a different way into carbohydrate (and fat ?). This has long been ascertained by clinical observations in diabetes [Külz], by the results of feeding animals poor in glycogen with protein [Naunyn, Külz], and by experimental investigations on animals treated with phloridzin, and on the dog after removal of the pancreas [von Mering and Minkowski (9)].

The number of investigations of this question is legion. But here, as in other departments, a distinction must be made between works which afford really useful material for the subject and others of less importance which certainly throw light, but in themselves offer no proof. A master of critical research, Pflüger, has recently shown the theory of sugar production from protein to be without foundation and entirely wrong. He has shaken one's faith in the trustworthiness of numerous experiments, especially of many of those which show that glycogen is deposited from protein. But out of the large number of investigations of the organism in diabetes many remain in which the formation of the sugar in the urine cannot be accounted for by "the carbohydrate of food, the glycogen and sugar of the body, the glucosamine and the "glucoside" of the body," etc. Certainly these investigations as to the falling of the respiratory quotient in diabetes, etc., also admit of the explanation that the sugar is formed from fat; Pflüger establishes this in the place of the theory of the protein formation of sugar. But in severe diabetes, whether natural or experimental, the very markedly increased excretion of sugar which accompanies the rise in the protein decomposition, and the correspondingly slight influence of the fats contained in the food, undoubtedly speak more for the formation of the new sugar from protein than from fat.

From which Elements of Protein does Sugar Arise ?

Only recently has research attempted to make clear the chemical mode of this transformation, this production of sugar from protein. The evidence that a carbohydrate group exists in almost every kind of protein, given by Pavy (10), seemed to clear up the whole question; the grape-sugar formed in the decomposition of protein exists preformed in it as such. It has been found that the sugar group of the protein, as that of the genuine albumins, consists almost entirely of glucosamine[1] [Friedrich Müller and his pupils, Seemann, Langstein, and Neuberg, etc. (10)], and is not identical with glucose. But the body must be credited with the power to transform glucosamine into grape-sugar, even though this has not yet been done in the test-tube.[2] The glucosamine, however, is not nearly sufficient to account for all the sugar formed from protein. Only the glyco-proteides, mucin, ovomucoid, and the mucoid substances of ovarian cysts, contain large quantities of it—25 to 35 per cent; the true simple protein bodies contain far less. Ovalbumin, the richest in carbohydrate, has at most 10 to 15 per cent., serum albumin and globulin only 1 per cent., muscle substance still less, and many, such at casein, are entirely free from carbohydrate. Even these yield glucose in large quantities, up to 45 and 60 per cent. of their original weight, in the diabetic organism, and from one-third to one-half of the protein carbon is thus converted into sugar [von Mering, Minkowsky, Halsey, Lusk (11)]. The sugar proceeding from protein is, therefore, not preformed in the protein molecule, but only comes into existence after a complicated process has taken place in it.

The Formation of Sugar from Amido-acids.

The following are the possibilities: either the hexoses proceed from protein nuclei containing at least six or more C-atoms, or else (either exclusively or at the same time) from combinations containing less than six C-atoms. In the last case a genuine C-synthesis would be necessary, not in the first.

Friedrich Müller (12) first gave expression to the idea that the grape-sugar came from leucin, whose mass far surpasses that of all the other cleavage products of protein. It is quite justifiable to straighten out the branched carbon chain in ordinary leucin (= isobutylglycocoll) into the plain one of grape-sugar. If 100 grammes of protein split off 30 grammes of leucin, under quantitative transformation these would yield 42 grammes of grape-sugar. Supposing that this 30 per cent. of leucin represents, at any rate for many proteins, a minimum, and that the lysin (diamino-*n*-caproic acid), as well as the leucin, could become grape-sugar, the possibility of a sugar formation entirely from chains with six C-atoms is mathematically proved—at least, for those cases in which the 100 grammes of protein do not give more than 40 to 50 grammes of sugar. Certainly there exist no experimental proofs for the change of leucin into sugar. In giving a leucin diet to animals, either with diabetes or freed from glycogen, neither R. Cohn nor Vamossy, nor Halsey, nor Simon came to any final conclusions (12). In none of these experiments was there so much glycogen in the liver or sugar in the urine that it could be fairly attributed to the leucin ingested, and to that alone.

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[1] C. Neuberg was the first to call attention to the presence of a true sugar group besides the glucosamine; afterwards Langstein isolated glucose from blood globulin. But it is a matter of very small quantities only, and their physiological meaning is still not quite clear (loosely-bound transport sugar?) (10).

[2] In the animal body glucosamine hydrochloride is not able to effect any formation of glycogen [Fabian and others (10)]. Nevertheless, the experiments so far conducted on animals do not altogether disprove the power attributed to the body of transforming glucosamine into glucose.

There is much to be said for the production of sugar from protein by synthesis from the lower carbon chains. Nebelthau (13), in an animal treated with phloridzin and fed with asparagin and acetamid, obtained an increase of sugar nearly corresponding to the amounts absorbed. Neuberg and Langstein consider lactic acid to be a first step, or one of the first steps, in the formation of glucose. In starving rabbits, after giving alanin, which soon becomes lactic acid, they found a somewhat large increase of glycogen in the liver (1 to 2 grammes after 20 to 30 grammes alanin). The building up of grape-sugar from lactic acid is the counterpart to the decomposition of sugar into lactic acid which once played so great a rôle, a "reversion" which no longer appears strange to us at the present day. But still, the glycogen amassed in the above case was not considerable enough to be attributed with certainty to the alanin supplied and to the lactic acid. The same must be said of Kraus's investigations of the sugar excreted after alanin was given to cats poisoned with phloretin. Embden and H. Salomon found, in accordance with Neuberg's and Langstein's suggestion, that there was an increase of the sugar excretion in a dog after removal of the pancreas which corresponded fairly with the alanin of the diet, and have thus substantially supported their idea.

But if the way from the protein to the grape-sugar does really pass through lactic acid, it would be necessary, since alanin is present in protein only in small quantities, for the other amino- and diamino-acids, as also for the leucin and the asparaginic acid, the lysin, etc., to be first transformed into lactic acid by oxidation and the splitting off of carbon atoms. It also remains to be considered whether a certain "formation of sugar from protein through synthesis" does not originate in chains with two carbon atoms. Paul Mayer observed the formation of grape-sugar from glycolaldehyde ($CH_2OH . CHO$) (13). Löw also supports this synthetical formation of sugar; with Pflüger, he believes the sugar molecule may be formed from CHOH groups by condensation.

(5). Fat from Protein.

That fat comes from protein owing to "fatty degeneration" is a view that must now be discarded. The intracellular fat which by this process becomes visible to the eye was in part there before but invisible—that is to say, not microscopically demonstrable by chemical means. But the far larger part of it has migrated into the cell, and owes its origin to fat first deposited in other places [G. Rosenfeld, Orgler] (*cf.* the section on the Fate of Fats). The formation of adipocere and the generation of fat from protein in maggots and in ripening cheeses are now considered doubtful. They found their chief support in Pettenkofer and Voit's (14) investigations in dogs, which formed fat from protein when they were fed exclusively upon the largest possible quantities of meat. A portion of the carbon from the decomposed protein remained in the body, and in the form of fat, it was supposed. Pflüger has attacked the authority of these experiments, as also that of all the other theories which support the formation of fat from protein, very keenly and with success; he and Rosenfeld showed the worthlessness of E. Voit's and Cremer's further investigations.

M. Gruber thereupon again published the results of two fresh respiration experiments lasting for eight days. In these a most marked retention of carbon from protein—as much as 197 grammes in eight days—took place. His results seem valid even making several corrections for error. The possibility of "a retention of carbon from protein" has been admitted ever since it has been known how soon the nitrogen splits off. Also, as sugar is formed from protein by very various methods, there is no theoretical objection to the formation of fat in some circuitous or direct manner. But practically it has nothing to do with the food and the growth of fat. Even with a copious meat diet there is only a slight increase of carbon, and this increase is deposited first of all as glycogen. The body only changes carbohydrate into fat—at least, so far as we know at present—when it is superabundantly supplied. According to Gruber, the large amount of protein carbon retained in his experiment had nothing to do with glycogen, but must have been deposited as fat.

The chemical problem of the formation of fat out of protein is contained in the questions of the making of sugar out of protein, and of the building up of fat out of sugar.

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3. The Simple End-products derived from Protein.

(*a*) Urea.

By far the greatest part of the nitrogen, about 80 per cent., reaches the kidneys for excretion in the form of urea. This is the chief metabolic end-product of protein changes in mammals. The figures vary somewhat according to the experimenter and the method employed. A simple and accurate method for the estimation of urea, apart from other substances, is unfortunately not available. The usual methods consist, generally speaking, of, first, the precipitation of a series of other nitrogenous bodies (by phosphotungstic acid, or by alkaline baryta mixture), and then, after a separate estimation of the ammonia, the quantity of nitrogen easily separable by acids or alkalis is found. The most accurate and at the present time most commonly employed methods are probably that of Pflüger and Schöndorf, and that of Mörner and Sjoqvist, the latter as modified by Salaskin and Braunstein.[1]

The old titration method of Liebig does not give, as was formerly believed, the quantity of urea, but shows approximately the total nitrogen. The absolute quantity of urea excreted daily is in reality parallel with the absolute amount of nitrogen in the urine, depending on the protein exchange. Only the relative value, the percentage which the urea bears to the total excretion of nitrogen, will be discussed here.

With animal diet the relative urea value is higher than with mixed or purely vegetable food. Schultze (1) found with flesh diet 88·2 to 88·6 per cent. of the total nitrogen as urea, with mixed diet 85·4 to 85·5 per cent.; Gumlich (1) with flesh diet 81·1 to 87·1 per cent., mixed diet 84·5 to 86·5 per cent., vegetable diet 78·4 to 81·3 per cent. After long-continued starvation (thirty days) the percentage of urea falls to 54 to 56 [O. and E. Freund (1)].

Not only the nitrogen of the protein is excreted as urea, but the protein decomposition products, glycocoll, leucin, tyrosin, also give rise to an increase of urea corresponding to their contained nitrogen [Schultzen-Nencki (2)]. This is also the case with asparaginic acid

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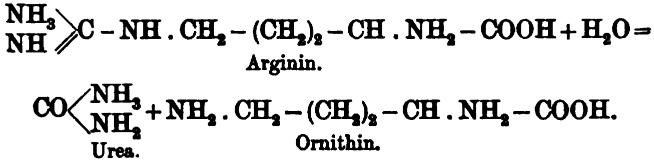
[1] For details of these methods the text-books of physiologico-chemical analysis must be referred to—Huppert's "Analyse des Harns," tenth edition, and Hoppe-Seyler and Thierfelder's "Chemische Analyse," seventh edition, Berlin, 1903.

[Knieriem] and ammonium salts (see below). The nitrogen of nucleinic acid is also, at least in part, excreted as urea [O. Loewi]. On the other hand, the nitrogen of certain substances—as, *e.g.*, acetamid ($CH_3-CO-NH_2$)—does not appear as urea, but this body passes, at least in the dog, through the organism unchanged [Schultzen-Nencki], while in the rabbit it is decomposed [Salkowski (2)].

Formation of Urea.

Part of the urea may come directly from protein without any complex processes, *i.e.*, without synthesis, by a simple hydrolytic splitting, that is, from such groups as contain, like urea itself, two atoms of nitrogen combined with one atom of carbon. This is exemplified in arginin from which urea is obtained directly by hydrolysis [Drechsel (3)].



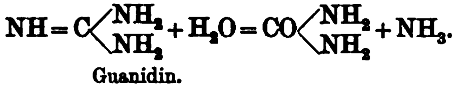
$$\underset{\text{Arginin.}}{\begin{matrix}NH_3\\NH\end{matrix}\!\!>\!C-NH.CH_2-(CH_2)_2-CH.NH_2-COOH}+H_2O=$$

$$\underset{\text{Urea.}}{CO\langle\begin{matrix}NH_3\\NH_2\end{matrix}}+\underset{\text{Ornithin.}}{NH_2.CH_2-(CH_2)_2-CH.NH_2-COOH}.$$

According to this author 9 per cent. of the total nitrogen in casein can be separated directly by hydrolysis in the form of urea. For other albuminous substances the percentage will vary according to their contained arginin. That arginin does in fact occur in the body as a free molecule (arising by autolysis ?) has already been pointed out [Gulewitsch].

Thompson fed dogs with arginin, and also injected it subcutaneously. In both instances 70 to 90 per cent. of the arginin appeared in the urine as urea.

In like manner other substances, introduced in the food or synthetically produced in the body, which, like arginin, contain the guanidin group, could in similar fashion yield urea by hydrolytic decomposition in the tissues—*e.g.*, kreatin [Hoppe-Seyler] and guanin [Kossel]:

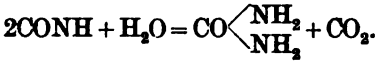


$$\underset{\text{Guanidin.}}{NH=C\langle\begin{matrix}NH_2\\NH_2\end{matrix}}+H_2O=CO\langle\begin{matrix}NH_2\\NH_2\end{matrix}+NH_3.$$

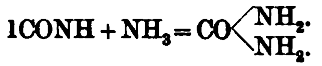
Further, it is possible that the purin bodies (xanthin, uric acid, etc.) as diureides yield urea directly by decomposition [Loewi (3) has confirmed Mörner and Sjoqvist's discovery that there is an absolute increase of urea after feeding with nuclein bodies], and in the same way the pyrimidin bodies as mono-ureides. The latter are present not only in nucleoproteides, but also as histidin in the molecules of all genuine proteins.

By far the greatest quantity of urea, however, arises not from a simple hydrolytic splitting of more highly constituted bodies, but owes its origin to a synthetic process. Only a few protein nuclei, indeed, contain, like urea, two nitrogen atoms combined with the corresponding carbon atoms, the majority having only one. A second ammonia or amido group must in all such cases combine with another residue which has one carbon atom combined with one atom of nitrogen. That the body may, in fact, produce ammonia in the urine is conclusively proved (see below), and that it forms ammonia in great abundance has been already shown.

There are various theories as to how this synthesis takes place. The least probable one appears at present to be the cyanic acid hypothesis put forward by Hoppe-Seyler and defended by Salkowski, which supposes urea to be formed by the union of two cyanic acid groups, or of one such molecule with a molecule of ammonia :



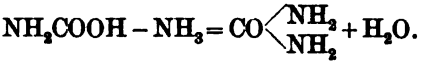
$$2\mathrm{CONH} + \mathrm{H_2O} = \mathrm{CO}\Big\langle\begin{matrix}\mathrm{NH_2}\\ \mathrm{NH_2}\end{matrix} + \mathrm{CO_2}.$$



$$1\mathrm{CONH} + \mathrm{NH_3} = \mathrm{CO}\Big\langle\begin{matrix}\mathrm{NH_2}.\\ \mathrm{NH_2}.\end{matrix}$$

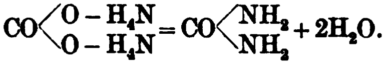
(Compare the objections of Schröder and Hofmeister.)

Nencki (4) considered carbamic acid to be the forerunner of urea, and believed urea to be formed from ammonium carbamate by the withdrawal of water :



$$\mathrm{NH_2COOH} - \mathrm{NH_3} = \mathrm{CO}\Big\langle\begin{matrix}\mathrm{NH_2}\\ \mathrm{NH_2}\end{matrix} + \mathrm{H_2O}.$$

This view received substantial support from Drechsel, who demonstrated the appearance of carbamic acid by the oxidation of amino-acids (arginin) *in vitro*. The hydration necessary for the formation of ammonium carbamate was explained by this author as due to alternating oxidation and reduction. After Drechsol had pointed out the presence of this acid in dog's blood, it was repeatedly demonstrated in blood and urine [Drechsel and Abel, Abel and Muirhead, Lieblein ; see also Hofmeister]. More recently Nencki, Hahn, and Pawlow have produced strong evidence in favour of this theory. They have found in dogs, with an Eck's fistula, a notable increase of carbamic acid. This theory closely resembles the teaching of Schmiedeberg, who believed that urea is produced from ammonium carbonate instead of carbamate by the withdrawal of water :

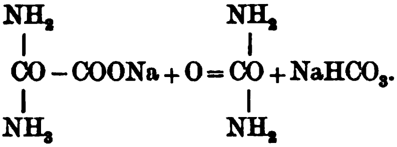


$$\mathrm{CO}\Big\langle\begin{matrix}\mathrm{O-H_4N}\\ \mathrm{O-H_4N}\end{matrix} = \mathrm{CO}\Big\langle\begin{matrix}\mathrm{NH_2}\\ \mathrm{NH_2}\end{matrix} + 2\mathrm{H_2O}.$$

If this abstraction of water occurred in two stages, then ammonium carbamate would be the intermediate substance.

Drechsel's views did not gain general acceptance, because the methods of determination employed were open to the objection that carbamates might be formed during the process. An accurate method by Macleod and Haskins (9) is now being applied to this aspect of the question. These workers state that the quantity of carbamate in a solution varies with the relations between the total $\mathrm{CO_2}$ and $\mathrm{NH_3}$.

According to Hofmeister, from whom emanates the latest theory on the formation of urea, the first occurrence is not the intermediate production of substances which, like carbamate and carbonate of ammonium, must in the change to urea first lose water, but the transformation of the second ammonia group takes place by " oxydative synthesis " somewhat according to the formula :



$$\underset{NH_3}{\overset{NH_2}{\underset{|}{\overset{|}{CO}}}} - COONa + O = \underset{NH_2}{\overset{NH_2}{\underset{|}{\overset{|}{CO}}}} + NaHCO_3.$$

As Hofmeister himself shows, there is between his theory and that of Schmiedeberg no great difference. If formerly the production of urea by the oxydative exhaustion of protein in the body presented difficulty because of the chemical differences, in so far as most observers had not succeeded in imitating this occurrence *in vitro*, this difficulty is now removed, since Hofmeister has succeeded in transforming protein and many other organic bodies at low temperatures outside the body into urea.[1]

Formation of Urea in the Animal Body from Ingested Ammonium Salts.—Current theories depend on the occurrence of ammonia in the animal body. That ammonia is produced in the organism from amido-acids and the like, and under what conditions it appears, has been described in an earlier chapter. The quantity of ammonia in the organs is by no means insignificant (see next chapter). Further, that the body really possesses the power of forming urea from ammonia is proved by numerous experiments, in which rabbits and dogs were fed with ammonia salts. The fact has also been demonstrated in omnivorous man in the same way [Lohrer, Knieriem, Salkowski, Feder and Voit, Munk, Hallervorden, Marfori, Coranda, and others (5)]. It is immaterial whether the ammonia is introduced as carbonate or formate, lactate, or citrate ; it always appears as urea in the urine, and indeed almost the whole quantity so appears, only a very small fraction being again excreted as ammonia.

Ammonium chloride is an exception to this rule (and also the sulphate and phosphate). In the dog [Feder, Salkowski, Munk (6)], and apparently also in man [Neubauer, Lohrer (6)], only a part of this—about 50 per cent.—is converted into urea ; the other half remains combined with the strong acid, and appears in this form in the urine. The quantities of ammonia taken by the mouth which the animal body can convert into urea are very considerable, up to 5 grammes of ammonia in a dog of 10 kilogrammes [Hallervorden ; even more according to Marfori], in man up to 10 grammes [Coranda, Weintraud (7)]. Whether the organism forms a single molecule of urea from each molecule of ammonium carbonate administered, according to Schmiedeberg's anhydride hypothesis, or whether from the two ammonia groups of ammonium carbonate, together with two carbon and nitrogen-containing groups produced in the body, two molecules of urea result, has not been established with certainty by the researches above described [*cf.* Schröder, Salkowsk i(8)].

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[1] In one direction, indeed, there is a substantial difference between Hofmeister's theory and that of Schmiedeberg. According to the teaching of the former, the carbon atom of urea would certainly be derived from the protein. On the other hand, the carbonic acid of the ammonium carbonate can quite well originate from the combustion of sugar or fat, and its oxidation product, the CO_2, may then combine with the ammonia of the protein. In this case the urea would have a " general origin." This theoretical consideration may be of importance for certain estimations—*e.g.*, as to the maximum amount of carbon which can be utilized from protein for the production of other substances (oxybutyric acid).

Place of Urea Formation.—V. Schröder's classical researches have shown that the liver is the chief seat of synthetic urea formation. When the blood of a starving animal is made to circulate through the liver of a starving dog, no urea is formed. On the other hand, considerable quantities are produced as soon as blood containing carbonate or formate of ammonium is substituted. This has also been completely established by Salomon for the liver of the sheep. The kidneys and muscles form, under like conditions, no urea. Recently it has been shown by Salaskin that the dog's liver not only forms urea from ammonium carbonate, but also from leucin, glycocoll, and asparaginic acid—that is to say, it may itself separate the ammonia necessary for the synthesis from these amido-acids. This fact agrees with the results of Loewi, Jacoby, and Lang, which show that the liver may transform firmly into loosely combined amido-acid nitrogen, so that it will yield ammonia by distillation with magnesium oxide.

Whether the liver is in mammals the only situation for synthetic urea formation is not yet certain, because Schröder's perfusion experiments have only been performed on liver, muscles, and kidneys. Experimental extirpation of the liver in mammals has so far led to no decisive result, because animals so operated on survive only for a short time. On establishing Eck's fistula in the dog, whereby the blood of the portal vein is diverted from the liver and led directly into the vena cava, the amount of urea diminishes from about 90 to about 77 per cent. [Nencki, Hahn, Pawlow (10)], yet the liver is not thereby totally excluded from metabolic processes. If, however, simultaneously with this operation, the hepatic artery is ligatured or the liver extirpated [Nencki, Pawlow, Salaskin and Zalesky], the relative quantity of urea diminishes so much (to 50 per cent. or less) and so continuously in the few hours that intervene before death takes place that the liver appears in every case as the chief organ for the synthetic formation of urea. The quantity of urea still excreted after the operation is absolutely very small, and might very well have been partly formed before the operation and excreted immediately after it. In part, however, it might also be due to the activity of the small fragment of liver remaining after the extirpation [Jacoby (10)]. But the possibility of urea synthesis taking place apart from the liver—and the Russian author himself is of this opinion—is not excluded by this experiment. Human pathology, which now and then furnishes more favourable conditions for the investigation than the most complicated experiments upon animals, assists in the settlement of this question. A substantial share in the production of urea by the liver in man is shown by the urea decrease in acute yellow atrophy of the liver and in phosphorus-poisoning. But any exclusive production of urea *by this* organ is strongly disputed by many authors [Lieblein and Munzer].

Fr. Pick found the quantity of urea greatly diminished in a case of intermittent bile fever without there being a corresponding increase in ammonia and amido-acids. He ascribed the failure of the urea formation not so much to the inability of the liver to synthesise the ammonia compounds, but rather to an interference with the decomposition or setting free the ammonia from the " nitrogenous dross " of the protein in the damaged liver (10).

Conditions of a Relative Diminution of Urea.—From the conditions for the production of urea already described we can partly conceive under what circumstances there may be a relative diminution of urea in the urine, and what nitrogenous bodies must then appear in increased quantities in place of the urea. We must consider (1) disturbances of the urea-forming function of the liver. Under physiological conditions there may be a weakening of this function, so slight that it need not be further referred to. But under pathological conditions, in the most severe acute and chronic lesions of the liver parenchyma in man, there are, chiefly in the last stages of life, conditions in which the disturbed liver function declares itself to the physician by a lowering of the urea production. The formation of this body is so eminently a " vital function " that life is extinguished before it is completely lost. Certainly, the quantity of urea in the last stage of acute yellow atrophy of the liver is greatly lessened, but probably not exclusively as a result of the inactivity of the liver for urea formation. A part of the urinary nitrogen appears in the urine for quite other reasons, not as urea, but as ammonia, because it is used for combination with organic and other acids (lactic acid) [Lieblein, Münzer, Salaskin and Zalesky (11)], a further part as " ammonsäure," and so on.

(2) Such a combination of ammonia with acids, which are introduced from without, is the second condition which leads to a relative diminution of urea, because even ammonia, by its combination with acids, is debarred from conversion into urea. The diminution of urea following an increase of ammonia through acidosis occurs in healthy men on a purely protein-fat diet, and pathologically under manifold conditions (*cf.* section on Ammonia).

(3) The relative amount of urea diminishes if proteins or metabolic products appear in greater quantity in the urine. To this category belong isolated cases of nephritis with abnormally large amounts of serum albumin and globulin, and also cases in which peculiar kinds of protein are excreted in large amounts [Bence-Jones, Magnus-Levy, Noel Paton, Salkowski].[1]

Still, it is for most purposes correct to leave the proteins quite out of account in considering the nitrogen contents of the urine. Of intermediate metabolic products which occasionally appear in great quantities in the urine, and whose appearance can reduce the normal amount of urea, leucin and tyrosin should be mentioned. They are chiefly observed in acute yellow atrophy of the liver. Their appearance in this disease is, however, as one may conclude from the experiments of Minkowski and Lang (13), as well as from the deductions of Lieblein and Pick, not so much to be referred to a disturbance of synthetic urea formation, but rather to primary disturbance in katabolism and oxidation. The organism is not in a position to decompose (*i.e.*, split off the ammonia[1]) and oxidize the amido-acids (which appear in many times abnormally increased quantity owing to the increased decomposition of protein).

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[1] In the cases here mentioned 35 to 70 grammes of albumin were excreted daily in the urine, the nitrogen of which accounted for 30 to 40 per cent. of the total urinary nitrogen.

Their appearance would then have to be regarded as parallel with that of cystin and diamine in the condition known as cystinuria and diaminuria. Again, in these disturbances of metabolism part of the nitrogen is withdrawn from its normal conversion into urea (by prevention of the splitting and oxidation). Yet the quantity of nitrogen which appears occasionally in the urine in the form of these last-named bodies is insufficient to reduce the relative amount of urea to any great extent. The same holds good for the cases in which there is a great increase of uric acid under normal or diseased conditions. Only in very rare cases of acute and chronic leuchæmia does the quantity of uric acid nitrogen rise from the normal (1½ to 2½ per cent.) to 6, 8, and 10 per cent.,[2] and lead to a corresponding diminution in the quantity of urea.

On what the diminution of the relative quantity of urea after a week's starvation depends [Freund (13)], and what substances here arise in place of the diminished urea, are questions to which there exists no satisfactory answer. An increase of ammonia plays a part in every case, the ammonia appearing in the urine in large quantity combined with organic acids, but the nitrogen accounted for in this way only covers a part of the diminution of the urea nitrogen.

The Urea Contents of Organs.—A substance which is excreted in such large amount as urea must also be demonstrable in the fluids and tissues of the body itself. As a matter of fact, it has been found by numerous observers in nearly every organ and fluid of the human and animal organism (14).

The quantitative methods employed have been, almost without exception, indirect, and are founded, following Bunsen's method, upon the recognition of the decomposition products of urea, ammonia and carbonic acid. All these methods, as v. Schröder pointed out, upon decomposition give too high values, because, besides urea, other nearly related substances yield ammonia and carbonic acid under approximately similar conditions. By separating and weighing urea in a pure condition Gottlieb and Schröder (14) found by the standard method the amount of urea in dog's blood to be 0·011 to 0·020 per cent., and in the liver 0·008 to 0·017 per cent.; the quantity increased distinctly during the digestion of flesh—in the blood to 0·028 to 0·055 per cent., and in the liver to 0·014 to 0·020 per cent. Urea could also be detected in the muscles, but only at the height of digestion. Schöndorf demonstrated urea in an extract of the muscles of a dog which was killed a few hours after a meal of 2,000 grammes of flesh, and identified it by estimation of the melting-point and by analysis. Apart from such digestive periods, it has been shown that normal muscles certainly contain no urea after perfusion of the products of protein cleavage in considerable quantity. The most prominent investigators, from Liebig to Nencki and Kowarcki, are agreed as to this. What was formerly described as urea in the organs and fluids was either not urea at all, or only a small fraction of it was this substance. The quantities of urea arrived at by indirect methods have, however, a certain value for purposes of comparison, because they have to do with substances which resemble urea, or are easily converted into it. Above all, they confirm the fact of the increase of urea during the period of protein digestion [Schöndorf]. The amount of the substances nearly allied to urea is of considerable importance. Schöndorf found that the chief parenchymatous organs of a dog of 32 kilogrammes, which was killed seven hours after a meal of 2,000 grammes of flesh, contained not less than 16·9 grammes of urea. The various organs, the muscles, blood, and glands contained about the same percentage of urea, approximately 0·12 per cent. The kidneys, as urea attracting and discharging organs, yielded the much higher figure of 0·67 per cent. For human blood Schöndorf gives the quantity of urea as 0·61 per cent. The striking feature, on a mixed diet, of Schröder's results is the fact that the liver, the urea-forming organ, contains a smaller proportion of urea than the blood. This circumstance shows unmistakably how uncertain are the conclusions based on the accumulation of a substance in an organ as to its formation in that organ.

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[1] Perhaps this ammonia splitting is also a chief or exclusive function of the liver. If, however, other organs also possess the same function, in equal or less degree, then the excretion of amido-acids does not depend only on disease of the liver.

[2] A case of acute leuchæmia excreted in twenty-four hours 28·7 grammes nitrogen and 8·7 grammes uric acid (=2·9 uric acid nitrogen) [Magnus and Levy (13)].

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(*b*) Ammonia.

The quantity of ammonia excreted daily varies in man, on a mixed diet, from 0·6 to 0·8 to 1·0 gramme [Neubauer, Knieriem, Coranda, Gumlich (11)]. It is lower on vegetable, higher on animal foods. In the daily urine there are—

	Coranda.	*Gumlich.*
On vegetable diet	0·400 gm. NH_3.	0·37 to 0·47 (NH_3) N.
On mixed diet	0·642 „	0·55 to 0·69 „
On animal diet	0·873 „	0·57 to 1·09 „

These figures show that the quantity of ammonia nitrogen bears a certain relation to the total nitrogen, of which it forms 3 to 5 per cent. With increased protein consumption the absolute quantity of ammonia also rises. In relation to the above figures, it must be observed that the various ingredients of a vegetable dietary differ in their effect on ammonia excretion, just as they do on metabolism throughout. The cereals, by their relatively high protein contents and absence of organic alkaline compounds, do not alter the acid reaction of human[1] urine, and they do not diminish the excretion of ammonia, or only slightly so, while green vegetables or fruits, with their high percentage of alkaline salts, do so in the most marked manner. On the other hand, the so-called animal diet used in such researches is, strictly speaking, always mixed, but with a larger proportion of flesh than usual; with a pure flesh-fat diet the ammonia in the urine becomes very much more increased, as we have already shown. The variation of ammonia excretion on different diets is also strikingly shown in different animals. In the normal dog about 5 per cent. of the total nitrogen excreted is in the form of NH_3 [Munk], in the rabbit only about 0·5 per cent. [Winterberg (2)].

1. *Influence of Acids and Alkalis upon the Excretion of Ammonia.*

If now, as explained in the foregoing section, the greater part of the ammonia produced in the body, as well as that introduced from without, is converted into urea, how is it that a small quantity of ammonia always appears in the urine as such and evades transformation into urea? Experimental investigation yields the following generally accepted explanation. The ammonia appearing in the urine serves exclusively—or, at any rate, in the first instance—to combine with the mineral acids which are set free in the body by the decomposition of protein and organic compounds of phosphorus appearing in the urine as salts, in so far as the fixed bases (Na, K, Ca, Mg) taken in the food and those set free in metabolic processes are insufficient for the purpose. In a purely vegetable dietary the excess of alkalis is so great that the sulphuric and phosphoric acids arising in the body are thereby fully neutralized, and there is still a surplus of alkalis, which appear as carbonates in the urine and make it alkaline. It is otherwise with flesh—and to a less degree also with cereals—and with mixed foods. Such a dietary is acid—*i.e.*, it yields on combustion in crucible or in the organism an acid ash, the ingredients of which are excreted to a large extent in the urine. Because, however, free acids do not pass into the urine, they combine, so far as there is not a sufficiency of fixed bases for the purpose, with the ammonia resulting from protein decomposition, and appear so combined in the urine.[2]

A complete analysis of the urinary acids and bases—such, for instance, as has already been made in cases of diabetes, and has yielded most useful information—should, in combination with a similar estimation of the fæces, yield still further results to pathology.

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[1] The urine of rabbits fed with oats is acid.

[2] Stadelmann and his pupil Hagentorn (following Gähtgens, who worked with the dog) have analyzed the total bases and acids of normal urine, and have calculated their sodium equivalents. They have shown that the sum of the acid equivalents considerably exceeds that of the fixed bases, and that the difference is covered, for the most part, by ammonia (in part, perhaps, by creatin and other substances not estimated which act as bases):

(*a*) Equivalent of acids =9·8949 grammes Na.
(*b*) „ „ fixed bases =7·7695 „ „
(*c*) „ „ „ „ $+NH_3$=3·1111 „ „
(*a*) to (*c*) excess of acid equivalent =0·7838 „ „

(Average from a five-day series by Hagentorn.)

The importance of ammonia as an acid-neutralizing factor is most convincingly proved by feeding experiments with organic acids and with alkalis. Walther (3) was the first to show that in dogs, after the administration of large quantities of hydrochloric acid, the ammonia in the urine was largely increased, about three-fourths of the administered hydrochloric acid reappearing in the urine combined with ammonia. This result has been confirmed by all subsequent investigators [Gähtgens, Auerbach, and others]. In man, also, after administration of mineral acids, there is an increase of ammonia. Hallervorden, experimenting on himself [assisted by Coranda (3)], found, after taking 2·81 grammes HCl for two days, an increase from 0·7 to 0·9 gramme daily to 1·1 to 1·31 grammes. The increased ammonia excretion lasted in this case for several days, as also at other times and under similar conditions.[1]

Organic acids lead to no increase of ammonia, because they, with the exception of benzoic and similar acids, undergo combustion in the body to form carbonic acid. There appear, however, in the metabolic processes under certain conditions organic acids which do not undergo combustion (*cf.* the chapter on Acetone Bodies), and these behave like mineral acids taken by the mouth, combining with ammonia to form neutral salts. When carbohydrate is totally excluded from the food and a purely flesh-fat diet is administered, large quantities of acetic and oxybutyric acids appear in the urine, and at the same time the ammonia is continuously increased up to 2·8 and even 3·3 grammes. It may then form 20 and even 26 per cent. of the total nitrogen [Gerhard, Schlesinger, Magnus-Levy (3)]. The above-named acids, and next to them lactic acid, also play a part in pathology as ammonia-exporting bodies. As in man, so in the dog, the introduction or formation of incombustible acids is met by increased excretion of ammonia. In the rabbit the neutralization of acids by ammonia does not occur [v. Walter (4)], or only to a very limited extent [Winterberg (4)].

Just as acids cause an increase of ammonia, so conversely alkalis lead to a diminution. The administration of 12 grammes of bicarbonate of soda lessened by about two-thirds the ammonia excretion in a dog, according to Hallervorden; while 10 grammes of acetate of soda reduced it to about a half or a fourth [Salkowski and Munk (5)]. Calcium hydrate acted in the same way as carbonates and organic salts of the alkalis [Abel and Muirhead]. The same results hold for the increase of ammonia in acidosis, due to organic acids in man. Gerhard and Schlesinger showed that the ammonia excretion, which on a purely animal diet rose to 3·3 grammes, returned to 0·8 to 0·9 gramme after administration of 20 grammes of bicarbonate of soda daily for several days. In the acidosis of diabetes (*q.v.*) and of other conditions the influence of alkalis on the excretion of ammonia is equally marked [Magnus-Levy (5)]. The ammonia which is in this way set free by the fixed bases from its combination with acids is converted in great part into urea, as has been fully explained in a previous section (5). It is a remarkable fact, and apparently in contradiction to the part played by ammonia as an acid-neutralizing substance, that the largest consumption of alkalis does not succeed in causing ammonia to disappear entirely from the urine, even if the urine in such cases has a strong alkaline reaction. Also, in the normal alkaline urine of the rabbit there are always traces of ammonia present. This apparent contradiction may be explained in this way: Even in the greatest flooding of the tissues with alkalis there is always ammonia present in the blood, because it is constantly being furnished anew by the organs, the change to urea taking place in the liver. A part of this ammonia is constantly circulating through the kidneys before it reaches the liver to be transformed into urea, and so it is that even in the presence of great excess of fixed alkalis, in the smaller quantities as in the greater, a small part of it always combines with the mineral acids of the blood, and thus is excreted as ammonia.

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[1] This statement should not be taken to mean that in the blood, etc., and in the urine, the ammonia actually remains in permanent combination with the hydrochloric acid. The actual combinations of several bases and acids with one another in a fluid cannot be inferred from their elementary estimation. The interchange of ingested salts in the organism with those already present has been studied by Bunge (4). Feder (4), with special reference to ingested ammonium chloride, has shown that it interchanges in the body with phosphates, somewhat according to the formula, $NH_4Cl + KH_2PO_4 = KCl + NH_4H_2PO_4$, and that next the chlorine of the ammonium chloride so introduced is excreted as potassium chloride in the urine, while the corresponding ammonia appears considerably later than the chlorine, combined at all events in part with phosphoric acid in the urine.

2. *Increase of Ammonia in Disturbance of the Functions of the Liver.*

A second cause which may lead to the increase of ammonia in the urine is the damage or loss of the urea-forming function of the liver. After total extirpation of the liver in geese the ammonia increases from a low percentage to about 69 per cent. and more [Minkowski, S. Lang (6)]. This rise is less marked in dogs and in man, apparently because in these life does not last sufficiently long after total exclusion or destruction of the liver to allow the characteristic changes to fully appear. Still, in a dog with Eck's fistula the ammonia rises to about 20 per cent. of the total nitrogen [Hahn, Nencki, and others], and quite as high in dogs in which, after the production of Eck's fistula, the liver has been extirpated [Nencki and Pawlow, Salaskin and Zaleski]. The same results follow in less degree on experimental destruction of the liver by the injection of acids into the bile-ducts [Lieblein]. In human pathology a few cases of severe disturbance of the liver have shown similar figures for ammonia in the last few days and hours before death (17·3 per cent. in acute yellow atrophy (Münzer); 15·6 per cent. in cirrhosis [Weintraud (6)]. If in the so-called acidosis the increase of ammonia is secondarily due to the circulation of increased acids, on the other hand, in exclusion of the liver the rise in quantity of ammonia is apparently—in part, at least—primarily due to interference with the synthesis of urea. This certainly follows only from what has been found in dogs with Eck's fistula. In these the urine, which is rich in ammonia and carbamic acid, is constantly alkaline in contrast to that in acidosis, which has an acid reaction, in spite of the increased ammonia. It is deficient in a corresponding increase of at least organic acids [Nencki and Hahn, Nencki and Pawlow, Salaskin and Zaleski (6)]. Less significant are the conditions in extirpation of the liver and in human pathology. Here the urine is, without exception, acid; the ammonia does not appear in the urine as carbonate or carbamate, but combined with organic acids and chiefly with sarcolactic acid [Minkowski, Lang, Salaskin and Zaleski, Münzer, Weintraud, and others; only Lieblein found it wanting in the acid urine of his dog]. And in these cases, as in genuine acidosis (*cf.* the chapter on Diabetes), it is only possible to make the urine alkaline by giving large doses of alkalis [Minkowski and Engelmann, Lang, Salaskin and Zaleski]. In a way as yet not quite clear at first sight, there are combined in this case the primary excretion of ammonia, due to interference with liver function, and the secondary increase, due to acid formation (6).

3. *Relative Increase of Ammonia in the Urine through Withdrawal of Alkalis.*

If by any means a portion of the alkalis which neutralize the mineral acids in the urine be withdrawn, then a percentage increase in the ammonia of the urine may occur. A withdrawal of fixed alkali must act on the relationships of the acidity and alkalinity of the tissues, in the same or in a similar manner as an increase of inorganic, or organic, non-combustible acids. Steinitz (6A) has brought forward the idea of a "relative acidosis,"[1] the occurrence of which had been previously conjectured by Keller, and attached it to that of the "real acidosis." In infants suffering from gastro-intestinal affections who received a large quantity of fat in their food he found considerably more alkaline earths and alkalis[2] in the fatty stools than usual, and as regards potassium, often even more than the food had contained. As, however, the body endeavoured so far as possible to maintain its relative alkalinity, the alkalis in the urine were markedly diminished, and ammonia appeared in increased quantity to take their place. It is not, however, by any means decided whether in such cases a genuine acidosis is not present at the same time in addition to the relative acidosis; it is, indeed, quite possible that, under these circumstances, organic acids are compelled to form a union with ammonia and participate in its increase. In any case, in gastro-intestinal disturbances of older children of two to ten years acetone and oxybutyric acid make their appearance just as in adults [Vergely]. This "increase in ammonia through loss of alkali" ought, however, undoubtedly to be much less frequent than that produced by pure acidosis (see the end of the chapter on Acetone Bodies). In healthy persons it will hardly ever be met with. The very slight increase in ammonia which Schittenhelm saw in adults after the addition of a large amount of fat to a mixed diet appears to me to be too insignificant to permit of any conclusions being drawn therefrom or of comparing them with the observations of Steinitz, as was done by the author; in fact, he has not indubitably demonstrated a loss of alkali by the stools. A relative acidosis is most likely to be met with when there is marked diarrhœa; moreover, in those instances in which it has not been produced by an excessive quantity of fat in the food, it may be that this is due to the fact that watery stools frequently remove a definite quantity of $NaHCO_3$ from the body. The same is the case when the fæces are passed through fistulæ in the lower portion of the small intestine. Under these circumstances, also, a relative acidosis may appear.

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[1] Assuming that the excretion of mineral acids in the urine normally attains a certain amount, the expression signifies an abnormal excess of such mineral acids over the fixed alkalis. Naunyn's pure acidosis signifies a fresh appearance of non-combustible organic acids (see chapter on Acetone Bodies). This difference must be kept in mind should the expression "relative acidosis" become current. "Relative acidosis" is a deficiency in alkalis [alkalipenia, Pfaundler].

[2] In order to place this teaching on an absolutely certain foundation a complete analysis of the total ash obtainable from the urine and fæces is necessary. In the first place—as is, indeed, probable—it must be shown that the alkali eliminated in the stool was united to fatty acids or CO_2, and not to inorganic acids—*e.g.*, Cl, P_2O_5—consequently, the alkalis may have left the bowel as such, and not as neutralized mineral salts. In the latter case neutral salts, and not "alkaline valencies," would have been withdrawn from the body. On account of the large amount of material which is required for such a complete analysis of the ash, experiments could be most suitably conducted on adults with profuse diarrhœa.

4. *Significance of a Percentage and an Absolute Increase in Ammonia.*

Fr. Müller (7) has pointed out that, in deciding upon an increase of ammonia, especially under pathological circumstances, the absolute increase only is of importance. The percentage amount of nitrogenous ammonia—that is, the quotient $\frac{(NH_3)N}{\text{Total N}}$—does not, he says, deserve consideration. This is correct, in so far as a raising of the absolute amount of ammonia frequently points to the presence of organic acids in the urine, and serves as a certain measure of their quantity. It is, however, by no means always the case, since the absolute amount of ammonia is not merely dependent on the formation of organic acids, but, in addition, on the degree of protein metabolism. A quantity of ammonia equal to 1½ to 2 grammes, which is decidedly abnormal for an exchange of 100 grammes of albumin, representing 16 grammes N and 2·5 grammes of SO_3, and which causes one to suspect the presence of organic acids, is quite a normal quantity for the decomposition of 180 to 200 grammes of albumin, which is represented by 5 grammes SO_3 in the urine. With the increase of the protein cleavage the absolute amount of formed sulphur acids rises also, and along with this the quantity of ammonia necessary for their neutralization.

With an ordinary mixed diet the relation of $\frac{(NH_3)N}{N}$ is about 3 to 5 or 6 per cent. Should it exceed 8 to 10 per cent., special reasons must be sought for to explain the occurrence. Under these circumstances the organic acids will usually be found in greater quantity in the urine, while in exceptional cases there will be an increase of the mineral acids. When in some diseases organic acids are not usually found and in others one does not meet with them regularly, although ammonia is present in increased amount, then the discrepancy is generally to be attributed to the deficient methods employed. (It is only in rare cases that the explanation is to be sought in the replacement of a pure by a relative acidosis.) A high percentage of ammonia points, almost without exception, to the presence of organic acids, even when the absolute quantity of ammonia is low (*cf.* the case of Nebelthau). On the other hand, if the absolute sum total of the ammonia is high, this does not by any means have the same significance. It is therefore desirable that the quotient should not be allowed to fall.

Further, in special cases with abnormally high acidosis and fatal acid intoxication it is interesting to know how much of the daily amount of nitrogen decomposed under the most favourable conditions appears as ammonia, and thus by neutralization is able to avert the harmful action of the acids. It seems tolerably certain that the amount of the nitrogenous cleavage is, to a certain extent, under these circumstances a measure of the absolute quantity of ammonia. The highest figures for human beings—7, 8, and 12 grammes of ammonia daily—have only been observed in diabetes in cases in which the breaking up of albumin and the total excretion of nitrogen in the urine (60 grammes) were unusually high [Stadelmann]. In none of these cases, however, was the quotient $\frac{(NH_3)N}{\text{Total N}}$ higher than 40 per cent., and higher values are just as seldom found in other physiological and pathological conditions—even in diabetic coma, for instance, in which a relative and absolute increase in the ammonia is always to be expected [Magnus-Levy (7)]. Only in one case, described by Nebelthau (7)—that of a fasting, hysterical woman—did the percentage of ammonia reach 66 per cent. This case, as a matter of fact, exhibits the smallest amount of nitrogen which, when disintegration of albumin is taking place, must circulate in the form of ammonia before it is changed in the liver into urea. As seen from the experiments by Minkowski on geese after extirpation of the liver, and from the observations in diabetic coma [Magnus-Levy], a cleavage of ammonia from completely formed urea does not appear to take place in life, or, at any rate, not to any considerable extent. The surviving liver does not lack the power to split off ammonia from urea [Jacoby] (7). If, therefore, in Nebelthau's case at least 66 per cent. of the total nitrogen appeared as ammonia, this accords with the acceptation previously mentioned—namely, that the nitrogen of the albumin does not appear first as an amide in combustion with carbon, but immediately as ammonia, and that the splitting off of nitrogen precedes the oxydation of the remaining carbon.

5. *Excretion of Ammonia by the Lungs.*

All the ammonia not changed to urea is ultimately excreted by the kidneys. Ammonia is not exhaled by the lungs, neither in the ordinary course of events, nor under those pathological and experimental conditions in which it circulates in increased quantity in the body. Neither with extirpation of the kidneys, and the subsequent injection of ammonium carbonate into the circulation [Lange, Biedl and Winterberg], nor in feeding with salts of ammonia [Feder and Voit], nor even in dogs with Eck's fistula [Salaskin], is that ever the case. This fact, ofttimes with certainty sustained, has been excellently demonstrated by Magnus, who was able to experimentally show the impermeability of the lungs for ammonia (8).

6. *The Liver prevents the Toxic Action of Ammonia.*

In conjunction with the statements made, a résumé of the teachings on the metabolism of ammonia and the rendering of it innocuous in the liver, as represented by the view of Nencki and Pawlow and their pupils, must be here undertaken. According to these investigators, ammonia is formed in all organs—at any rate, it is present in all—possibly as the carbamate. By the use of improved methods (freeing of ammonia with magnesia), Salaskin and Zaleski demonstrated the following amounts of ammonia in the organs of dogs during fasting and after feeding:

In 100 *grammes.*	*Fasting Dogs.*	*Dogs after Feeding.*
	Milligrammes, NH_3.	
Arterial blood	0·42	0·41
Blood of peripheral veins	0·8	0·7
Blood of portal vein	1·29	1·85
Muscle	14·4	12·9
Brain	11·2	12·0
Kidneys	15·1	14·8
Pancreas	21·2	22·1
Spleen	19·5	14·6
Liver	17·5	23·3
Mucous membrane of stomach	29·1	36·5
Mucous membrane of intestine	18·7	32·4

Winterberg in 100 c.c. of human venous blood found 0·9 milligramme, and H. Strauss, in the transudation from a case of cirrhosis of the liver, met with slightly higher values (9).

In the tables given above the following points are of importance and worthy of consideration: (1) The small amount of ammonia and its constancy in arterial blood; (2) the larger quantity of ammonia in the blood of the portal vein in comparison with that in the arteries and the peripheral veins; (3) the greater amount in the organs (ten to twenty times). During digestion the quantity of ammonia in the liver, in the mucous membrane of the stomach and intestine, and in the portal vein rises, whilst in most of the other organs, and more especially in arterial blood, it remains much the same. Owing to the liver, by the formation of urea, rendering innocuous the ammonia which is always passing into the blood in abundant quantities from all the organs, the constancy and the low value of ammonia in arterial blood is thereby guaranteed. If the blood, however, by the interposition of Eck's fistula, be diverted from the liver, it reaches the general circulation with its poisons undiminished—that is to say, containing a larger quantity of ammonium carbamate, which then may exert its noxious influence. So long as the decomposition of albumin and the consequent formation of ammonia in the body is kept low by a deficiency of protein in the food, marked disturbances in the general conditions of the animals do not occur. If, however, flesh be given to the animals experimented on, the contents of the arterial blood as regards ammonia rise to the height of the values which are met with at other times in the portal vein, and then there arises the picture of poisoning by carbamates, which leads to a fatal termination with coma, catalepsy, and amaurosis [Nencki-Hahn-Pawlow]. The amount of ammonia in the brain of a dog killed in this manner is increased in an extraordinary degree.[1] [Nencki-Pawlow]. In dogs with Eck's fistula, the introduction of ammonium carbamate produces poisonous symptoms identical with those arising from the administration of flesh. In dogs, on the other hand, which have not been operated on, this substance does not cause any toxic symptoms, since it is changed with sufficient rapidity by the liver (9).

It is to be remembered that Biedl and Winterberg have raised important objections against this teaching of the exclusive action of the liver in rendering the ammonia innocuous. It is impossible, however, to enter here into the details of their experiments (9).

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[1] In this work the quantities of ammonia are in accord with the older methods furnishing high values (liberation of ammonia by lime). The relative values, however, which demonstrate an increase in the ammonia, are still correct [Saleskin-Zaleski].

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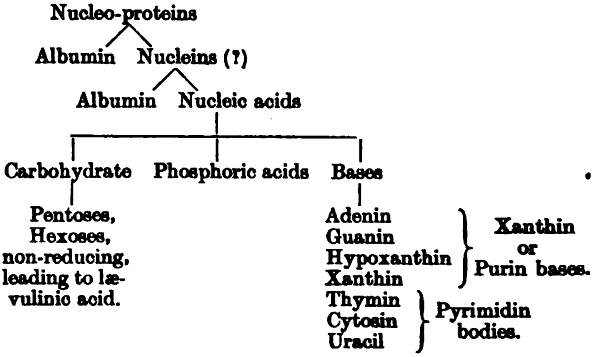
(*c*) Uric Acid and Purin Bases.

The Nucleo-Proteins.

The composition of the nucleo-proteins—or at least of their derivation products, so far as they are known at present—is shown in the following schema:



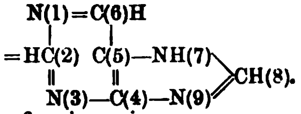
It is still undecided whether the so-called "nucleins" are chemically preformed as intermediate products between the nucleo-proteins and the nucleic acids, or whether they are merely unstable disintegration products of albumin through nucleic acids. The name "nuclein" is unfortunately often used in the literature on metabolism for the nucleo-proteins as well as for the nucleic acids, a custom which readily gives occasion for confusion.

In connection with the above schema it must be noted that—

1. The pentose of the nucleo-proteins of the pancreas and liver is the *l*-xylose. The amount of the pentoses arising from nucleo-proteins in the human body reaches at least 10 grammes.

2. Between the nucleic acids and the phosphoric acids there are still somewhat complicated organic phosphoric acids, like thyminic acid.

3. The xanthin or purin bases are in organic combination, and not in the form of salts. Apparently xanthin and hypoxanthin are not present as such in the nucleo-proteins, but arise first through adenin and guanin. The relations of the "purin bodies" to one another, amongst which must be placed uric acid, are shown in the following summary:

	Purin ..	$=C_5H_4N_4$	=  N(1)=C(6)H HC(2) C(5)—NH(7) CH(8). N(3)—C(4)—N(9)
Aminopurin	Adenin ..	$=C_5H_5N_5$	=6-aminopurin.
	Guanin ..	$=C_5H_5N_5O$	=2-amino, 6-oxypurin.
Oxypurin	Hypoxanthin	$=C_5H_4N_4O$	=6-oxypurin.
	Xanthin	$=C_5H_4N_4O_2$	=2.6-oxypurin.
	Uric acid	$=C_5H_4N_4O_3$	=2.6.8-trioxypurin.

When the amido groups are saturated with oxygen, adenin is transformed into hypoxanthin, and guanin into xanthin. The oxydation of hypoxanthin gives rise to xanthin, and that of the latter to uric acid.

The following summary shows the occurrence and relations of the methylated xanthin :

Caffein	=1.3.7-trimethylxanthin		in coffee and tea.
Theobromin ..	=3.7-dimethylxanthin		
Theophyllin ..	=1.3 ,,		
Paraxanthin ..	=1.7 ,,	from caffein	in the urine.
Heteroxanthin ..	=7-monomethylxanthin	from theobromin and theophyllin	
Unnamed ..	=1- ,,		
,, ..	=3- ,,		

Uric Acid.

The metabolism and excretion of uric acid is independent of the ordinary nitrogenous economy; it follows laws of its own. If at one time it was thought that uric acid should be considered other than as a product of the intermediate metabolism of albuminous bodies in general, its exact source could not be identified. The investigations of Horbaczewski, and the comprehensive inquiries into the chemistry and physiology of metabolism during the last decade, have for the first time shed some light on its origin and fate.

Uric acid arises in the body of sucklings—at any rate, for the most part—from the oxydation of the nuclein bodies of the food and those of the body, but partly from preformed nuclein bases. Just as we now ought to completely omit many of the old hypotheses, so we must discard many of the numerical results previously obtained by defective methods, such as the hydrochloric acid precipitation method [Heinz]. Since it yields too low values, we can only use its figures when they show enormous increases. The methods of precipitating the uric acid by silver [Salkowski and Ludwig], as well as those which are based on the insolubility of urate of ammonia [Fokker, Hopkins, and others], are alone really utilizable. The different methods in which uric acid is directly estimated by titration, without previous isolation in the urine, certainly do not give reliable values.

The Production of Uric Acid from Nucleins.

Horbaczewski (1) found that during the digestion of organs containing blood—*e.g.*, the spleen, liver, and other glands—xanthin bases arise if air be excluded, whereas if air be passed through during the process uric acid is formed. According to his view, the antecedent stages leading to the production of both substances are the same—viz., from the nucleins of the organs.[1] By feeding men and rabbits with such bodies he was able to bring about an increase in the uric acid excreted. In many previous and simultaneous experiments by other investigators an increase was in most instances not found, but that was owing to the fact that the majority of the experiments were conducted on dogs, in which animals the metabolism of nuclein differs essentially from that which obtains in men. Horbaczewski's teaching, however, first obtained general recognition when Weintraud (1), by feeding with glands rich in cells, observed a ready means of markedly influencing the excretion of urea. After feeding with ¾ to 1 kilogramme of thymus gland Weintraud found as much as 2·5 grammes of uric acid in the urine. In the same manner other glands rich in cells—*e.g.*, the liver, kidneys, and especially the pancreas—gave a constant and marked increase of uric acid [Umber, Burian and Schur, Smith, Jerome, Hopkins, Walker Hall, Rockwood, and many others]. After giving 1½ kilogrammes of pancreas, Lüthje observed that the excretion of uric acid in a diabetic patient rose to 6·7 grammes. The isolated nucleic acids also produce an increase in the uric acid excreted, just like the nucleo-proteids [Minkowski, O. Loewi (1)].

Horbaczewski had originally taken up the position that only the bases in organic combination with the nucleic acids, and not those which are free, are oxidized to uric acid. According to him, the body could only transform the former into uric acid. It has, however, been necessary to reject this somewhat mystical view. Organic extracts of the spleen, liver, etc., are able to oxydize the free bases (xanthin and hypoxanthin [Spitzer, Wiener (2)], guanin and adenin [Schittenhelm, Jones and Partridge]), into uric acid, and a similar change is effected by the introduction of the free bases into the body of living persons. According to our opinion this is proved—at any rate, for hypoxanthin [Minkowski, H. Strauss, Burian and Schur, Krüger and Schmidt, Sivèn, Hall, and others]. As regards the other bodies (xanthin, adenin, and guanin), it has been shown to be very probable [Burian and Schur, Schittenhelm and Beudix, Krüger and Schmidt]. Both the last-mentioned authors saw in men:

Of 3 grammes hypoxanthin	62 per cent.
„ 0·6 gramme adenin	41 „
„ 1·5 grammes xanthin	10 „
„ 0·6 gramme guanin	traces

transformed into uric acid in the urine. The greatest difficulty is seen in the transformation of free guanin into uric acid; after 7·1 grammes of guanin Burian and Schur could not be sure of any increase in uric acid. The " combined "guanin oft he nucleo-proteins of the pancreas, however, is to a great extent changed into uric acid [Lüthje, O. Loewi (2)]. Walker Hall has shown that guanin, in the form of powder, or in thymus or pancreas glands, is not absorbed by the intestinal cells to any extent. From the fæces he obtained and isolated the greater part of the guanin and adenin contained in the food. These results have been recently confirmed by Schittenhelm.

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[1] *Cf.* the résumé of the composition of nucleo-proteins on p. 110.

In contradistinction to the bases mentioned, the methylated xanthin bodies (caffein, theobromin, and theophyllin) cause an increase of the nuclein bases in the urine, but do not influence the excretion of uric acid [Minkowski, Burian and Schur, Krüger and Schmidt (2)].

The transformation of adenin and guanin into hypoxanthin and xanthin is brought about by de-amidization, the change of the latter substances into uric acid being an oxidation process. The amino group is split off by means of the ferments guanase or adenase [Schittenhelm, Jones and Partridge]. The oxidation is effected by means of an oxydase, the "xanthinoxydase." This oxidation is the only clear example of the significance of oxidizing ferments in the disintegration of nitrogenous substances in the body.

From all these experiments it is evident that uric acid is chiefly derived from the nucleins. It is an easy matter to prove that it only arises from them, and not also from the disintegration of simple albuminous bodies. An excessive addition of albumin free from nuclein to an ordinary diet does not at all affect the amount of excreted uric acid, even though the nitrogenous metabolism is increased [Hess and Schmoll, Burian and Schur, Kaufmann and Mohr (3)]. The experiments of Hirschfeld and Sivèn (3) are in this respect most convincing. Both made use of albumin free from nuclein, the input being considerably varied. With an excretion of nitrogen of 5 to 20·1 grammes Hirschfeld observed that the values for uric acid fluctuated between the narrow limits of 0·386 to 0·492 gramme. Sivèn found with—

Food Albumin.	*Urinary Uric Acid.*
18 grammes.	433 milligrammes.
25 "	449 "
80·9 "	442 "
145·3 "	478 "

Since the independence of the purin metabolism from the general nitrogenous interchanges has been established, the calculation of the relationship between the uric acid excreted and the total nitrogen, to which a certain significance was formerly attached, has lost in interest. We understand to-day that the quotient $\frac{\text{Total N}}{\text{Uric acid N}}$ can fluctuate in its furthest limits from $\frac{25}{1}$ to $\frac{126}{1}$ [v. Noorden (3)]. A consideration of the diet is now of importance in view of these relationships.

Exogenous Uric Acid.

Uric acid chiefly arises from the nucleo-proteins and purin bodies present in the food. This portion is described as exogenous uric acid. It has long been known that the excretion of urea is higher from an animal than a vegetable diet, the fact being explained by the larger amount of uric-acid forming material contained in the former. Not only do the nuclein-rich glandular organs contain large quantities of combined purin bases, but considerable amounts of free xanthin bodies, especially hypoxanthin and xanthin, occur in the usually eaten flesh meats.

According to Burian and Walker-Hall, and Burian and Schur (3), there are contained in—

100 grammes of fresh thymus ..	0·429 to 0·482 gramme of purin-N.
„ „ „ pancreas ..	0·123 „ 0·183 „ „ „
„ „ „ ox flesh ..	0·055 „ 0·071 „ „ „
„ „ „ milk ..	0·0004 „ 0·0006 „ „ „
„ „ „ black bread..	0·010 milligrammes „ „
„ „ „ potatoes ..	0·0005 to 0·0006 grammes „ „
White bread, rice, eggs, salad, cabbage	0 to a trace.

The vegetable food of civilized men contains but small amounts of purin bodies except the pulses [Walker Hall]; nucleic acids are also found in the vegetable kingdom (3). Purin bodies are also present in beer and porter [Walker Hall].

Endogenous Uric Acid.

A second source of the urinary uric acid arises from the nuclein bodies in the tissues, a certain amount of which is always undergoing disintegration. The excretion of uric acid does not cease even after thirty days' abstinence from food [O. and E. Freund], though it falls rapidly when the food is withheld. In two individuals Schreiber and Waldvogel found

	Milligrammes of Uric Acid.	
On the last day of eating	477	—
„ first day of starvation	290	718
„ second „ „	233	405
„ third „ „	197	205

Even the infant, receiving only traces of purin bases in the milk, excretes large quantities of uric acid, as much as 100 milligrammes daily [Goeppert (4)].

This uric acid, arising from the disintegration of the nuclein bodies in the tissues, has been designated *endogenous* in contradistinction to the exogenous, which originates in the nuclei of the food. Its amount may be approximately determined by feeding on a milk and vegetable diet poor in purins. The values of the endogenous uric acid thus received are probably at a minimum, since the body apparently restricts the interchange, when the substitution of nuclein substances in the food is wanting [Loewi]. The following amounts have been noted:

	Uric Acid.	*Uric Acid. Nitrogen.*	*Purin-N (Uric Acid N + Bases-N).*
	Gramme.	Gramme.	Gramme.
Burian and Schur	—	—	0·120 to 0·200
Kaufmann and Mohr	—	—	0·120 to 0·209
Bonnani	0·22 to 0·265	0·07 to 0·08	—
Sivèn	0·44	0·15	—
Herrmann	0·48	0·16	—
Hirschfeld	0·39 to 0·49	0·13 to 0·16	—
Schreiber and Waldvogel (third starvation day)	0·197 to 0·205	0·066 to 0·068	—

Burian and Schur lay special emphasis on the great difference in the values of the endogenous purin-N excreted by different persons, and maintain that these values are peculiar to the individual. On the contrary, the interchange of the food-purins is quite independent of this, different individuals, according to these investigators, always excreting the same percentage of the food-purins as urinary purins. O. Loewi goes even further, and denies any influence, as regards the individual, on the excretion not only of the exogenous, but of the endogenous uric acid. He maintains that different healthy persons on identical food always excrete the same amount of uric acid so long as their metabolic equilibrium is maintained. On the other hand, Schreiber and Waldvogel, as well as Kaufmann and Mohr, show, by careful personal investigations, that the excretion of exogenous and of endogenous uric acid undergoes marked personal fluctuations in different individuals, and a review and examination of other experiments previously reported completely bears out the correctness of this view (see also the later investigations on the uric-acid diathesis) (4).

Quite recently Burian (4A) has shown that the endogenous uric acid does not by any means only arise from nucleo-proteins—that is, from the destruction of nuclei. In the human body such destruction is not extensive enough to produce the quantity of purin bases necessary for the daily formation of 0·3 to 0·6 gramme of endogenous uric acid. From Burian's investigations it appears that endogenous uric acid arises from free purin bases present in muscle tissue. It is not necessary that the hypoxanthin of the muscles should have previously existed as a nucleo-protein substance, forming an ingredient of nuclei in other organs, before its entrance into those muscles. Burian attributes to the metabolism in the muscles a large share in the formation of the endogenous purins in the urine of breast-fed animals.

Absolute Quantity of Uric Acid excreted.

Daily excretion of uric acid:

On a diet composed of vegetables, and purin-free	about 0·25 to 0·6 gramme.
„ mixed diet	„ 0·5 to 1·0 „
„ diet containing much flesh meats	„ 1·0 to 1·5 or 2 grammes.

The amount rises as the quantity of flesh is increased. R. Orgler excreted—

During starvation	480 milligrammes of uric acid.
With 600 grammes of flesh	809 „ „ „
„ 800 „ „	758 „ „ „
„ 1,650 „ „	1,230 „ „ „

Beef-tea, the extract of flesh, has the like effect. After taking 1 litre of bouillon, Sivèn observed that the uric acid rose from 0·34 to 0·79 gramme; and H. Strauss, after 50 grammes of extract of meat, from 0·45 gramme to 1·05 grammes. By the ingestion of glands rich in nuclei (see above) the amount excreted may reach 2, 3, or more grammes. In general, females excrete less uric acid than males, since they usually consume less meat. With few exceptions, no conclusions as regards possible disturbances of the purin metabolism can be drawn from the absolute quantity of uric acid excreted without considering the nature of the food eaten (5).

Destruction of Uric Acid in the Body.

The difficulties concerning the correct interpretation of this special metabolism are still further increased by the fact that the uric acid in the body is not constant, but is in part further decomposed, and not wholly excreted unchanged. If fully formed uric acid is introduced into the body, it is to a large extent burnt up [Stokvis, Garrod, Stadthagen, Schreiber and Waldvogel, Weiss, Weintraud (6), and others]. The same is undoubtedly true for the exogenous uric acid in the body arising from the food as well as for the endogenous [Burian and Schur]. Sodium urate injected under the skin does not apparently behave the same in different persons. Of 0·86 gramme to 1·3 grammes of uric acid injected subcutaneously, Burian (6) excreted 50 per cent. unchanged in the urine, while Ibrahim (6) observed 99 per cent. (?)

The first change in the process of the disintegration of uric acid is apparently one of oxidation. This step is not, however, definitely ascertained, since the first catabolic product is not yet identified. According to Burian (6A), the oxidizing ferment which brings about the destruction of uric acid is not identical with xanthin oxydase. In man, at any rate, the disintegration of uric acid proceeds as far as urea; in dogs, however, in many cases only to allantoin [Salkowski, Minkowski, Theodor Cohn, Mendel (6)]. Certainly it does not seem to be proved, as stated by Burian and Schur, that a definite portion (in men about 50 per cent.) of the uric acid formed in the body is destroyed, and that the other 50 per cent. which passes by the "kidney-filter"[1] before further combustion ensues, is excreted. Undoubtedly at different times and in different persons very variable quantities of the uric acid which has been formed undergo oxidation.

The most various causes, therefore, have to be considered in connection with a change in the uric acid excretion. An increase in the uric acid may be due to: (1) an alteration in diet—*e.g.*, a larger amount of purins or improved conditions for absorption; (2) an increased destruction of nuclein material in the body; (3) a diminution in the further combustion of the uric acid formed. It may, however, originate (4) in an increased washing out of uric acid retained, perchance, in the body; and finally (5) by a possibly increased "uric-acid synthesis" in the body. On the first point see p. 114. The possibilities mentioned under (2), (3), (4) can only be discussed briefly here, but the question of a "uric-acid synthesis" requires a more detailed consideration.

2. In connection with the increased metabolism of nuclein-containing material one ought not nowadays, as Horbaczewski did, to think only of

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[1] There is no doubt that the varying amount of uric acid flowing directly by the kidney filter is not the only cause influencing excretion.

a destruction of the white cells circulating in the blood. That part of Horbaczewski's teaching which attributed all uric acid exclusively to the destruction of the nuclei of the leucocytes has been sufficiently refuted. The increase in the uric acid is frequently much too large to be explained by the often small, or even absent, "hyperleucocytosis." Undoubtedly in acute leuchæmia an increased formation of endogenous uric acid from the destruction of nuclei does take place;[1] here, however, there is a destruction not only of the white cells of the blood, but without doubt also of the spleen, lymph glands, etc. Besides, one must, according to Burian (4A), also consider the possibility of an increased formation of endogenous uric acid from the free purin bases in the body.

3. There are, indeed, certain indications gained from experiments on animals, etc., that an increase in uric acid may proceed from deficient disintegration of uric acid already formed; still, in an individual case it must be a difficult matter to establish this as a factor in human pathology.

4. In healthy individuals there are no proofs of a more lengthy retention of formed uric acid and of the possibility of its being later flushed out of the system; but its antecedents—the nucleic acids and nucleo-proteins—seem, at any rate, able to remain in the body for some time. After taking calves' spleen and similar substances an increase in the uric acid excreted is often seen to appear and to last several days. On the contrary, a temporary retention and even an increased flushing out of uric acid only seems to occur in diseased conditions—as, for instance, in gout.

The Synthetic Formation of Uric Acid.

Finally, in addition to those circumstances influencing the excretion of uric acid there arises the further question of the possibility of a synthetic formation of uric acid in breast-fed animals and in human beings. It has on several occasions already been stated that the body can form nucleo-proteins, and therefore also nuclein bases from a diet free from nuclein [Miescher, Kossel, Burian and Schur (7)]. The substance out of which they arise is still quite unknown. Naturally, from these synthetically produced purin bases uric acid can occur afresh in the body, and the system in breast-fed animals possesses the power of forming uric acid synthetically in this way as well as via organized nuclear material. As a rule, however, the question is whether such uric acid has been synthetized in the sense that it can have been constructed directly from lower catabolic products of albuminous bodies—*e.g.*, glycocoll or urea—without previous transformation into purin bases and nucleo-protein.

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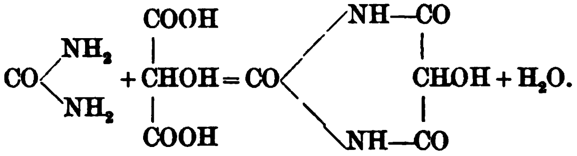
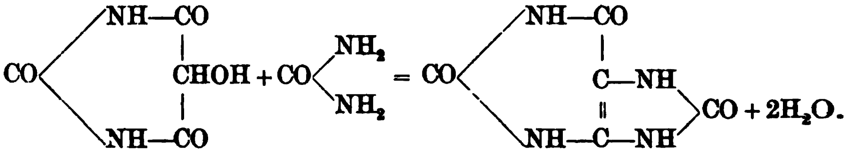
[1] We are not here considering the question—which is, moreover, not always clearly defined—whether in leuchæmia, etc., the increased purin excretion originates from a vital process, in the sense that the metabolism of the leucocytes not undergoing disintegration or of the round cells of the organs raises the uric-acid interchange, or whether the destruction of those cells only produces uric acid. The latter is, at any rate, placed beyond doubt by certain observations in acute leuchæmia. Still, the first-mentioned possibility cannot at present be excluded with certainty.

Birds and reptiles which excrete 60 to 70 per cent. of their nitrogen as uric acid do to a large extent accomplish a synthetic formation of uric acid. In them only a small part of the total uric acid excreted arises by disintegration of nuclein substances through oxidation [Minkowski, Mach (8)]. The major portion of the uric acid is of synthetic origin. Whether the birds are fed with amino-acids, urea, or salts of ammonium, the liver forms uric acid out of all these substances [Knieriem, Jaffe and H. Meyer, Schröder]. According to Wiener (8), the uric acid is here produced from urea and tartronic acid, dialuric acid arising as an intermediate product.


Tartronic acid. Dialuric acid.


Dialuric acid. Uric acid.

When both substances were administered simultaneously to fowls, the excretion of uric acid always rose to the amount one would have expected. Feeding also with other acids containing three carbon atoms —*e.g.*, lactic, malic, and mesoxalic acids—gave the same result; they must, however, first change into tartronic acid by oxidation or reduction, since this is the immediate antecedent of uric acid [Wiener].

Wiener also states that in breast-fed animals a synthetic formation of uric acid occurs from the same substances as in birds. According to him, there is merely a quantitative and not a qualitative difference in the uric-acid metabolism of the two classes of warm-blooded animals. In both uric acid may arise by disintegration of nucleins from oxidation as well as by synthesis. It is simply that in breast-fed animals the synthetic formation is of slight extent, and is usually obscured by the preponderance of the disintegration process. Nevertheless, Wiener has been just as little successful, as was previously Minkowski, in proving a uric-acid synthesis in breast-fed animals when feeding experimentally with tartronic acid, lactic acid, and similar bodies. The administration, also, of various substances containing the pyrimidin ring, and therefore in close relationship to the purin ring, does not produce in dogs an increase in the excretion of uric acid [Steudel]. Wiener thought that he was able to establish a uric-acid synthesis from tartronic or dialuric acid and urea, at any rate, in the extracts from the liver of cattle. The increase of the uric acid in his experiments, however, did not arise from a synthesis of the substances given, but by oxidation of already-formed xanthin bases [Burian (6A)]. If these are previously removed from the liver xtracts, uric acid can no longer be obtained by digestion with dialuric cid and urea.

If, therefore, one must retain the possibility of a uric-acid synthesis n breast-fed animals, it must be pointed out that as yet there is not any listinctly supporting evidence available in its favour.

Uric Acid Diathesis.

The question, already mentioned, of an individual difference in the metabolism of purin bodies has a close connection with that of the occurrence of a uric-acid diathesis, and leads to the inquiry as to whether there are persons in whom the metabolism of purin bodies shows essential quantitative or even qualitative variations from that seen in healthy individuals. In this connection it must be pointed out that in certain persons uric-acid values are observed which far exceed the limits of the physiological fluctuations in uric-acid excretion. On a vegetable diet Lehmann (18) excreted 1 gramme of uric acid,[1] and Dapper's (18) servant, undoubtedly a perfectly healthy man, also on a vegetarian diet, had a daily output of 0·79 gramme. The behaviour of the man experimented on by G. Rosenfeld and Orgler (18) is in favour of the presence of a uric-acid diathesis. After taking 500 grammes of thymus, he excreted on an average 2¼ grammes of uric acid, on one day even over 3 grammes! These are figures which, with equally large quantities of calf's sweetbread, have never been attained in the numerous investigations on other men. The most striking results, however, were the after-effects of thymus ingestion. Even ten and twelve days afterwards Orgler excreted enormous quantities of uric acid—with a mixed diet, 1,400 and 1,600 milligrammes, and on a flesh diet, 1,243 instead of 768 milligrammes. It is remarkable that Orgler during starvation had not excreted much more uric acid on the second day than other men on a diet free from purins (374 milligrammes; on the first "butter day," 392 milligrammes). The abnormal increase in the excretion appearing after the calf's sweetbread certainly did not depend on a flushing out of material which had been retained. Whether it arose merely from an increased interchange of endogenous nucleins, or whether, possibly, from a normal formation of exogenous and endogenous uric acid whose further combustion was delayed, cannot be decided from the evidence. It is possible that investigations on such persons might materially advance the question of a synthetic formation of uric acid in men. At any rate, the experiments of Rosenfeld and Orgler establish with certainty the occurrence of an altogether abnormal excretion of uric acid in a man who up to that time had shown nothing unusual in this respect.

Situation where Uric Acid is formed and disintegrated.

In birds the liver is the exclusive site for the synthetic formation of uric acid. As Minkowski's (9) classical experiments have shown, after extirpation of the liver, the uric acid disappears from the excrements save for mere traces [see also S. Lang (9)]. Its place in the excretions is taken by ammonia and *d*-lactic acid, and not by those substances —urea and tartronic acid—which, according to Wiener, give rise to uric acid.

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[1] Determined by Heinz's method, and therefore a low value.

Perfusion of the liver of the goose with ammonium lactate (also with arginin) positively demonstrates the uric-acid forming function of the liver of birds [Kowalewski and Salaskin (9)]. On the other hand, the formation of uric acid from nuclein bases by oxidation is not confined to the liver. In birds, after excision of the liver, hypoxanthin is transformed into uric acid [v. Mach (9)]; in mammals, also, formation of uric acid may take place in most organs, certainly always in the chief glands (liver and spleen). The surviving organs or their extracts possess the power of transforming nuclein bases into uric acid, and, in fact, as Spitzer and Wiener showed, without the coexistence of putrefaction, which was originally accepted as a necessary factor. Where a process like this is so apparent (it behaves like a simple oxidation), it is certainly correct to accredit the living organ with the same capabilities as the extracts from organs which act fermentatively. A formation of uric acid has been lately proved by Burian (4A) in living muscle, it here arising from the oxidation of hypoxanthin.

The same organs which form uric acid are also able to destroy it. Formation of uric acid by oxidation is easily demonstrated during autolysis of the liver. It occurs to a large extent in the pig and dog, and less so in cattle [Stokvis, Ascoli, Jacoby, Wiener (9)]. In the living dog the share taken by the liver in destroying uric acid can be clearly shown, for the uric-acid excretion rises when its destruction is prevented by removal of this organ[1] [Nencki and Hahn, Burian and Schur]. The renal tissues of all mammals during autolysis in the test-tube are able to decompose uric acid [Wiener, Schittenhelm]. Muscle also possesses the same capabilities [Wiener, Burian, Schittenhelm], although, according to Wiener, this occurs only in the ox, and not in the dog.

The differences in the metabolism of purin bodies in the dog as compared with man may be dismissed in a few words. In the dog administered nuclein substances (thymus, pancreas) are followed by the excretion of but little uric acid. Instead of this allantoin chiefly appears in the urine, and, in fact, in large quantities (up to several grammes), just as after giving uric acid and hypoxanthin [Salkowski, Minkowski, Th. Cohn (10)]. In man, under similar conditions, this substance does not occur, or at least only in very minute quantities. In man, allantoin is more thoroughly destroyed than in dogs [Minkowski, Loewi, Poduschka]. In rabbits the capacity for destroying uric acid, though greater than in man, is still decidedly less than in dogs [Burian and Schur]. In them the metabolism of uric acid yields glycocoll. In man, the intermediate products of the metabolism of uric acid have not as yet been isolated. They may, in so far as they become oxidized, be chiefly transformed into urea (10).

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[1] Lieblein (9) readily refers the increase of uric acid from administration of acids, after destruction of the liver, to a circulation of excessive quantities of nuclear material containing nuclein.

Action of Different Substances on the Excretion of Uric Acid.

Glycerine, Fat, and Carbohydrate.—Glycerine in very large doses (up to 200 grammes) produces a rise in the excretion of uric acid from 0·67 gramme to 1·15 grammes (Horbaczewski and Kanéra (11)]. These observers found, as did Mohr and Kaufmann subsequently, a decrease of uric acid after the addition of butter or sugar to the ordinary food. Still, very large doses were necessary in order to render this effect evident (about 300 grammes of cane-sugar and 200 grammes of fat), and the diminution of uric acid did not amount to more than 60 to 80 milligrammes, corresponding to from 6 to 10 per cent. of that previously excreted. According to Hermann (11), there was no change after giving butter. In contradistinction to the above observers, Rosenfeld and Orgler (11) invariably observed an increase of uric acid after giving much butter and sugar; still, their results cannot be applied to healthy individuals, as the person employed in their researches was a subject of "uric-acid diathesis."

Effect of Imbibition of Water and Alcohol.

An extensive flushing of the body with water does not exert any evident action on the amount of excreted uric acid during proportionate feeding, the latter essential factor being but rarely fulfilled throughout experiments performed. Schöndorf (12), "with regular food," found after administration of—

Ordinary food minus water ..	.. 1·181 grammes of uric acid in the urine.
" " with 1 litre water	.. 1·143 " " " " "
" " " 2 litres "	.. 0·932 gramme " " "
" " " 4 " "	.. 1·016 grammes " " "

These fluctuations lie within the limits formerly recorded. Other observers obtained similar results. Thus, Laquer and Schreiber found that the uric acid excretion rose but slightly after giving 1 to 3 litres of water. Burian and Schur observed that the dog, during artificial diuresis, excreted more purin during the first few hours, but in the course of twenty-four hours the normal balance was regained.

The imbibition of alcohol also appears to have no striking action on the excretion of uric acid (v. Noorden, H. Leber, and others). G. Rosenfeld alone maintains the contrary (13). In man he found an increase of 70 milligrammes (= 14 per cent.) in the excretion of uric acid after giving 70 and 130 grammes of alcohol. Standing as he does in the front rank of the scientific combat against alcohol, he expressed the conviction that alcohol "certainly spares the actual albumin of the body, but in its hypocrisy makes fearful ravages amongst the nucleo-proteins." One can hardly agree to this explanation of the vast increase of uric acid, especially when one considers the brevity and the number of his experiments. Rosemann, from the results of the researches of his pupil Haeser, and those of Hermann and others, comes to the conclusion that one to two bottles of wine and whisky and champagne do not substantially influence the excretion of uric acid. In fact, after the administration of alcohol the increases or decreases observed by him disappear when compared with the differences arising day by day in the alcohol-free series of experiments.

Numerous drugs have been tried with regard to their action upon the excretion of uric acid, especially in gout. Salicylic acid, for instance, possesses a decided action. Customary doses (3 to 6 grammes) are followed by an increased uric acid output, both in healthy and diseased persons, up to 2 to 3 decigrammes and more [Bohland, Magnus-Levy, Ulrici (14), and numerous others]. In all cases the effect passes off after a few days, but it becomes re-established on increasing the medicinal dose [Schreiber and Zaudy]. The action of salicylic acid is also evident when with a vegetable diet only a little exogenous purin circulates in the body [Schreiber and Waldvogel (14)]. Even in vegetarians who have not tasted meat for a number of years the effect of the salicylate is shown by an immediate increased uric acid excretion in the urine, and thus the endogenous uric acid is at issue [Walker Hall]. The excess of uric acid excreted must arise endogenously. When the administration is stopped, a marked diminution of uric acid follows, and this persists for a longer period than that of the excess excretion. It is not yet decided whether this increase of uric acid is due to excessive flushing of the tissues, or to an increased metabolism of nuclear material by a sort of toxic action, or to diminished combustion. The numberless other agents to which one has, perhaps without justification, ascribed an action on uric acid excretion, can find no consideration at this place. The action of quinic acid alone deserves a brief mention, as it touches upon an important theoretical question. Weiss (14) considered he had found that quinic acid markedly diminished the uric acid excretion, and explained further that it combined with glycocoll, after being transformed into benzoic acid. As this glycocoll, according to his meaning, is the source of synthetically formed uric acid, then it ought to reduce the amount of uric acid, owing to its being otherwise employed. The theory of a synthesis of uric acid from glycocoll in the body is, as yet, however, not supported by experimental proof, and other observers find that very large doses produce no diminution at all in the uric acid excretion [Weintraud, Lewandowski, Ulrici (14)].

Carbonate of lime, in daily doses up to 22 grammes, does not influence the uric acid excretion [J. Strauss (15)]. Large doses of alkalis affect it very slightly. They evoke, only occasionally, a slight diminution of uric acid [Salkowski, Stadelmann and his pupils, Hermann (15)]. The effect of muscular exertion is considered elsewhere.

The Presence of Uric Acid in the Blood.

Uric acid, like all substances which are formed outside the kidneys, but excreted by them, occurs in the blood in traces too small to yield reactions with the ordinary tests. Such is only possible when it is present to the extent of 1 milligramme in 100 c.mm. of blood. While uric acid cannot be demonstrated in the blood of the dog, ox, and horse, the results in healthy man are various. Von Jaksch and Klemperer were unable to find it; Garrod, Abeles, and Petrén (16) found quantities insufficient for quantitative determination. These small amounts fall far short of those met with in certain diseases, such as leuchæmia, gout, nephritis, etc. [Garrod, v. Jaksch, Magnus-Levy]. Experiments have taught us to recognise various possibilities as to the causes at work in an accumulation of uric acid in the blood. Thus, Weintraud found 5 milligrammes of uric acid (about 9 milligrammes of xanthin bases) in 100 c.mm. of human venous blood after the ingestion of a large quantity of calf's sweetbread. It behaves here like a surplus overflow, for it shows that the power of the kidneys to excrete uric acid is generally not very great. The normal daily quantity (about 1 gramme), when gradually formed, is so rapidly removed within the twenty-four hours that traces are scarcely to be met with in the blood. On the other hand, 2 to 3 grammes are daily formed after the administration of thymus nuclein, and the excretion lingers a corresponding time after the formation. Secondly, there comes into consideration a prevention of the excretion. Burian and Schur have shown that, in the dog at least, extirpation of the kidneys does not lead to a recognisable accumulation of uric acid in the blood, as in this animal the liver completely destroys the retained uric acid. Immediately this organ and the kidneys become detached from the circulation uric acid accumulates in the blood. The relationships in man are apparently otherwise, his powers of destroying uric acid being far behind those of the dog; for severe disturbances of the kidneys readily lead to accumulation of uric acid in the blood and tissues (16).

The Purin Bases.

The excretion of the purin bases in the urine and fæces has for long arrested the attention of investigators, the easily-applied method of Krüger-Wulff being in general use. Much toil and expense have been expended on these investigations. The method, however, yields much too high results, and is quite useless, while comparative investigations are completely worthless. We can only consider as authentic such values as have been obtained by the silver method [Camerer, Salkowski, and others]. According to these, the amount of the xanthin bases in the daily urine amounts to from 15 to 56 milligrammes [Salkowski, Flatow, and Reizenstein (17)]. It is somewhat higher according to Camerer (18 to 48 milligrammes of nitrogen bases) and Krüger-Schmid (16·6 milligrammes of nitrogen bases in a sixteen-year-old boy). According to Burian and Schur, 4 to 27 milligrammes are found in the urine with a purin-free food (without coffee and tea), and 30 to 40 milligrammes of nitrogen purin bases with a mixed diet. The quantity of these bodies rarely amounts to more than 8 per cent. of the uric acid excreted at the same time [Salkowski]. Only a small part of these, small quantities as they are, originate with a mixed diet from the actual nuclein bases, xanthin, hypoxanthin, and adenin (guanin is absent from normal urine). According to M. Krüger and G. Salomon (17), only 23 per cent. of the combined bases can be isolated from the urine. The main amount (over 70 per cent.) arises from methylated xanthins (para-, hetero-, and 1- methylxanthin), which originate in the organism by the splitting off of methyl groups from the caffein and theobromin of our food [Albanese, Gottlieb, and Bondzynski]. The nuclein bases, combined with nucleic acid and non-methylated nuclein bases which are introduced in the food, are chiefly oxidized into uric acid, or even further, only an imperceptibly small proportion contributing to an increase of the urinary bases. Further, by the administration of large quantities of the pure bases in man, only a small proportion is excreted unchanged [Burian and Schur, Krüger, and J. Schmid]. In the dog, adenin leaves the body, for the greater part, as such [Kossel, Minkowski]. The teaching that uric acid and purin bases could be mutually substituted in the urine, which was for long defended, is not now tenable. We do not know of an "alloxur-bases diathesis" (17).

A larger quantity of the xanthin bases occur in the fæces (Weintraud). Krüger and Schittenhelm found 53 milligrammes of nitrogen bases (= 100 milligrammes of bases) in the excrement of a dog which excreted only 16·6 milligrammes of nitrogen bases in the urine. Uric acid has also been found both in the meconium, and in the fæces of adults [Weintraud, Galdi]. The purin bodies of the fæces originate partly from unabsorbed nuclein substances in the food. This explains their increase after administration of such substances as calf's sweetbread. Some nucleins, such as those of sweetbread, are only with difficulty decomposed in the human intestine and absorbed. Guanin and adenin are absorbed with difficulty, and thus appear, like the nuclein in the sweetbread, to a large extent in the fæces. Hypoxanthin and xanthin are easily absorbed, and only occur in traces in the fæces. They also arise partly from epithelial nuclein substances separated from the mucous membrane of the bowel, since they have been found after food free from bases, and in the meconium (Weintraud), and in the secretions poured into the intestine from pancreas, stomach, etc. It thus occurs here, not from a distinctive metabolism, but from an unavoidable loss of organic material from the internal lining of the body analogous to the shedding of the epidermis (17).

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(*d*) Creatinin.

The creatinin of the urine arises chiefly from the creatin of muscle tissues. Muscle contains about 0·15 to 0·3 per cent. of creatin [Voit]. After large doses of meat (1,500 grammes) an excessive increase in the creatinin of the urine occurs (up to 4 grammes and more) [Voit, Gruber]. Creatinin appears to be almost beyond assimilation, as after feeding with pure creatin or creatinin almost the whole (60, 95, 100 per cent.) appears in the urine, and, in fact, almost exclusively as creatinin [Meissner, Voit, Mallet]. The excretion is almost completed within twenty-four hours [Mallet, Gruber (1)]. Creatin is always found in addition to creatinin in urine which is alkaline when passed. According to Folin (2), creatin is not quite absent even in normal acid urine.

The presence of creatinin exclusively in muscle—the musculature of man contains about 90 grammes—and its almost complete resistance to the action of other substances in the organism, permit creatinin to appear as a special product of muscle metabolism. Still, one can scarcely comprehend it as a worthless waste product of albumin metabolism in muscle, as its constancy and its amount in muscle are too great. In muscular work with much exertion the excretion of creatin in the urine rises greatly (compare the chapter on Muscle Work). Observations on progressive muscular atrophy show that the creatinin of the urine, as distinguished from that taken in the food, originates essentially from muscle, being formed there from other substances. In severe cases of this disease the quantity of creatinin is reduced to a decigramme [Langer, Jakabowitsch, Weiss (3)].

With a mixed diet about 0·8 gramme to 1·2 grammes of creatinin are excreted daily [Neubauer, Ph. Munk, C. Voit (4)]. It is less with vegetable diet (0·43 gramme [K. B. Hofmann], 0·61 to 0·86 gramme [Munk]). Macleod obtained decidedly higher values—namely, 2·098 grammes with " mixed meat diet," and 1·064 grammes with a " creatin-free " food—and distinguishes between an exogenous and an endogenous creatin. Long found 0·91 gramme in vegetarians. Women excrete less creatinin than men. In a suckling infant it is completely absent [K. A. Hofmann (4)]. Creatin does not disappear in fasting. Baldi (5) found, in the case of Succi, 0·801, 0·716, and 0·403 gramme on the seventh, twelfth, and seventeenth days of fasting—certainly remarkably large quantities. The creatinin nitrogen constituted 3·2, 3·7, and 2·4 per cent. of the total nitrogen. After the seventeenth day of fasting the creatinin sank markedly. Since the suckling child upon a creatin-free food forms creatin in the developing muscles, and while plant-eating animals persistently excrete creatinin, the organism doubtless possesses the power of forming creatin from the albumin of the food. (Ordinary albumins do not yield creatin, but myosin does. Hence creatinin may be certainly considered as a metabolite of muscle albumin.) It is not yet known whether the diamino acids serve as material for this, or whether the nitrogen of the monamino acids become utilized for this purpose.

Klercker (*Hofm. Beitr.*, 1906, S. 59), working with Folin's valuable colour method, has determined the quantitative variations in the endogenous creatin and creatinin output. An addition of 225 grammes of meat did not materially affect the creatinin excretion ; larger quantities led to the appearance of more or less creatin egestion, while of the creatinin ingested a relatively higher percentage occurred in the urine. Klercker considers that these flesh bases are independent of one another, both being in part utilized by the tissues and in part excreted unchanged in the urine.

Koch (*Amer. Journ. of Physiol.*, 1905, 15, p. 15) suggests that creatinin is an index of methyl metabolism in the body, and that under ordinary conditions of diet the methyl groups of the lecithin and cephalin ingested can all be accounted for by the methyl groups of the creatinin excreted. Folin (*Amer. Journ. of Physiol.*, 1905, 13, pp. 84, 118) regards urinary creatinin as an index to a certain kind of protein metabolism, the amount of creatinin eliminated depending upon the weight of the individual and upon the amount of his muscular tissues. Van Hoogenhuyze and Verploegh (*Z. P. C.*, 1905, 46, p. 14), Pekelhering ("K. akad. v. Wetenscappen," Amsterdam, 1905), and Klercker (*B. C. P.*, 1906, viii., p. 59) confirm Folin in his contention that while the creatinin output is a constant quantity which varies with the individual, it is wholly independent of quantitative changes in the total amount of nitrogen eliminated. Noel Paton (*J. P.*, 1905, 33, p. 1) found a certain relationship to be present in the dog between the production of creatinin and the nitrogen intake. Closson, using Folin's colorimetric method, which is now almost everywhere considered to be most satisfactory, obtained uniform excretion of creatinin in children and in suckling animals and in vegetarians, and further confirms the view that creatinin is a characteristic endogenous, catabolic end-product.

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(*e*) Hippuric Acid.

Benzoic acid when circulating in the body combines with glycocoll, and removes for combustion this "intermediate product of albumin metabolism" which otherwise succumbs to complete oxidation. The synthesis of these two substances to hippuric acid follows in the kidney, at least in the dog, as Bunge and Schmiedeberg have shown, and in plant-eating animals in other organs also [Koch, W. Salomon, Hofmann]. Wiechowski (8) and Magnus-Levy (8) have independently shown that glycocoll, in the form of hippuric acid, occurs in larger quantities in the urine of vegetable feeders than was preformed in albumins. The particular manner of its origin from albumin is not yet clearly detailed. Moreover, the kidney of the dog contains a ferment (the hystozyme) which breaks up the hippuric acid again [Schmiedeberg (1)].

The extent of this synthesis is limited by the quantity of glycocoll present at the time in the tissues or arising from the decomposition of albumin during the circulation of the benzoic acid ("glycocollvorrat" [Wiener]). Wiener's idea of a glycocoll store is now given up. According to Wiener and Cohn, as much as 0·8 gramme of benzoic acid per kilogramme in the rabbit is combined to form hippuric acid, and thus "deprived of toxic action"; any further benzoic acid is excreted uncombined. It does not unite with other amino-acids, such as alanin and leucin, to form benzoyl-alanin or -leucin. Yet, according to Wiener, the amount of hippuric acid ought to increase after administration of leucin if the latter is transformed into glycocoll. Since the formation of hippuric acid is limited, only certain quantities of benzoic acid become deprived of toxic properties; therefore Wiener means that the breaking up of albumins does not yield much leucin, because glycocoll would originate regularly from the leucin, and much greater quantities of hippuric acid be thus formed. The cleavage of albumin in the body therefore produces bodies which are not identical with those produced by ferment action. This conclusion is not convincing. Feeding with gelatin containing glycocoll produces more hippuric acid with administered benzoic acid than by feeding with glycocoll-free casein. From this Cohn concludes that only the glycocoll preformed in albumin enters into combination; that which arises by oxidation—at least, that from higher amino-acids—does not so combine. Still, according to Wiener, glycocoll can originate in the tissues from uric acid. Experiments on plant-eating animals, however, decidedly denote an origin of hippuric acid from higher amino-acids [Magnus-Levy (2)].

Besides appearing in combination with benzoic acid in the urine, glycocoll appears in the bile combined with cholalic acid. According to O. Zimmermann, the total glycocoll in man ought to be eliminated in the bile. Thus, he could find no hippuric acid in the urine of a patient with a complete biliary fistula after administering benzoic acid. S. Rosenberg refuted these results in the dog. The bile of this animal, however, excretes at most only small quantities of glycocholic acid, so that Zimmermann's interesting results in man and in plant-eating animals still await confirmation.

The daily amount of hippuric acid varies considerably. On a chiefly milk diet it amounts to 0·1 to 0·3 gramme [Lewin (4)]; with mixed food, 0·7 to 1·0 gramme; with vegetable food and a liberal supply of fruit and green vegetables, 1 to 2 grammes and upwards.

With vegetable feeding there are numerous aromatic products present, the more important of which are cinnamic acid, hydro-cinnamic acid, quinic acid, etc. These are oxidized to benzoic acid, and give rise to hippuric acid. After doses of 20 to 25 grammes of quinic acid the hippuric acid excretion in man rises to 3-6 and even to 6-8 grammes [Lewin, Förster (5)].

The second source of benzoic acid is from albumin decomposition in the intestine. Phenylalanin, which is transformed into phenylpropionic acid, becomes further oxidized into benzoic acid (see Aromatic Bodies). Therefore hippuric acid is not absent from the urine with a purely meat diet, and similarly during fasting, so long as the large intestine contains nitrogenous matter which is capable of undergoing decomposition. The hippuric acid completely disappears from the urine of the dog only after thorough intestinal disinfection with calomel [Baumann (6)]. Of greater significance, though as yet not clearly explained, is the fact that in ruminants the administration of "easily digestible substances" (ground beans, starch, sugar, oil) diminishes the hippuric acid excretion [Henneberg and Stohmann, Weiske]. In the experiments of Pfeiffer and Henneberg on sheep, the 13 grammes of hippuric acid which are usually excreted in the urine on feeding with meadow hay, completely disappeared when an addition of 170 grammes of albumin[1] was administered. After withdrawal of the albumin the hippuric acid reappeared to the same extent as previously (7). Albumin thus may have this effect, even though it furnishes glycocoll to the preformed benzoic acid.

The origin of hippuric acid is a classical example of those syntheses in the body where the result is a neutralization of toxic characters. In this way substances which do not generally appear as metabolic end-products (or only to a limited extent) are always at hand for the purpose of combining with toxic agents. One regards these as "intermediate products of tissue change." Many of them—ammonia, for example, which serves for the neutralization of mineral acids, sulphurous acid, and so on—may be obligate links of intermediate tissue change; while others—such as glycuronic acid—are only formed when necessity arises. Sulphuric and carbamic acids may be also mentioned as compounds which are employed in the syntheses of toxin neutralization. In all these complex compounds one must clearly distinguish the primary or toxic from the secondary or non-toxic; an incorporation of the former produces the syntheses, a part not played by the secondary compounds.

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[1] Recently contradicted by Rieke (7a).

(*f*) Urobilin.

Urobilin is a derivation of the pigmentary constituents of hæmoglobin. The iron-containing hæmatin splits off from oxyhæmoglobin to the extent of 5 per cent., and from hæmoglobin may be obtained hæmochromogen (reduced hæmatin). The next derivative is the iron-free hæmatoporphyrin, which only appears in the urine during pathological conditions ; it changes readily into bilirubin, which is apparently isomeric. This transformation occurs in the liver [Naunyn and Minkowski (1)], and only rarely outside that organ—such as in the tissues after extensive blood extravasations [Latschenberger, Quincke].

The amount of bilirubin discharged daily by the bile into the intestine amounts to about ½ gramme in man, according to Stadelmann. Still, this estimate, like that of the bile-acids, is decidedly doubtful. Stadelmann denies a reabsorption of unchanged bile-pigment from the intestine —that is to say, a " circulation of bilirubin."

In the intestine the bile-pigment becomes reduced to stercobilin or urobilin by the putrefactive bacteria—in fact, exclusively by the processes of decomposition [Macfadyen, Nencki and Sieber (2)]. Under normal conditions the reduction is complete, and the pigment passes out in the fæces as urobilin, and not as bilirubin or biliverdin. Unchanged bile-pigment appears in the excrement in diarrhœa, since the period of putrefaction is shortened. The meconium of the newly-born contains no urobilin, since the intestine is free from bacteria up to birth [Fr. Müller].

A proportion of the urobilin becomes reabsorbed, and is again partly excreted by the bile, the major portion, however, being eliminated in the urine. In the healthy organism the urobilin of the bile and the urine originates exclusively from the intestine, as a reduction of the bile-pigment occurs there only, and not in the tissues. If no urobilin is formed in the intestine, then none is passed in the urine. It disappears completely from the urine both in the dog and man, if the bile-duct be blocked, but it reappears again after feeding with bile [Fr. Müller]. On stopping the supply of bile it again disappears. The same applies to the origin of the urobilin excreted in the bile [Beck]. The urine of the newly born contains no urobilin, since none is formed in the intestine [Fr. Müller (2)].

The exclusive origin of urobilin from the intestine has been with certainty confirmed for the healthy adult, but the same does not hold good under pathological conditions. In blood extravasations into the tissues, in obstruction of the bowels, and, above all, in febrile diseases with cachexia, the excretion of urobilin in the urine may be excessive. Here the question arises whether a formation of this substance takes place within the tissues, either directly from blood-pigment or from bilirubin. This can be readily denied in the case of the urobilinuria after hæmorrhages. One may conclude, from the analogies of numerous experiments, that the free blood-pigment is carried to the liver, and is there transformed into bile-pigment. In this " pleiochromia " the greater part of the bilirubin secreted gives rise in the intestine to increased formation of urobilin [Quincke (3)]. On the other hand, the increased urobilin excretion in the urine of febrile patients is referred to an " endogenous " origin by careful observers, and apparently with justification [Quincke, D. Gerhardt]. Observations by Magnus-Levy may be cited in support of this view. He noticed that in autolysis of the liver, with the exclusion of putrefaction, considerable quantities of urobilin appeared. Gilbert and Herscher also record the formation of urobilin on adding minced kidney to solutions of bilirubin (3).

Under normal conditions, F. Müller found 83 to 89 milligrammes of urobilin in the fæces, and as much as 20 milligrammes in the urine (with an exclusively milk diet, as well as with a purely meat diet). Other observers report higher figures for the urine—Saillet, 30 to 130 milligrammes; and G. Hoppe-Seyler, 80 to 140 milligrammes. The differences may perhaps be referred to the fact that the urobilin is present in the excretions, not only as such, but also in varying quantities as urobilinogen [Saillet, O. Newbauer (4)]. The constitution of this body is unknown. It apparently is related to hæmopyrrol, a decomposition product of the reduction of hæmatin, which was discovered by Nencki and Zaleski. It is converted readily into urobilin on adding acids, or to a body which gives this reaction, and which may be changed to urobilin in the organism. Thus it appears that hæmatin may be transformed without the intermediate formation of bilirubin. It has not been ascertained whether this actually occurs in the body.

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(*g*) Other Nitrogenous Substances in the Urine.

After the estimation of urea, uric acid, and ammonia, there remains a nitrogenous residue whose quantitative analysis has as yet been unsuccessful in every instance. Various procedures serve at least to divide it up somewhat further, and thus permit a review of the mixed nitrogenous substances in the urine. They are founded essentially on the separation by means of phosphotungstic acid—a method already employed by Schöndorf and Gumlich. In the phosphotungstic precipitate and filtrate, the nitrogen is separated into portions either "easy or difficult to split up" (Pfaundler). The following scheme gives the substances which fall under the different headings according to Pfaundler :

Phosphotungstic Precipitate. (a) Easy to split off the N	*Phosphotungstic Precipitate.* (b) difficult to split off the N	*Filtrate.* (a) Easy to split off the N	*Filtrate.* (b) difficult to split off the N
ammonia	diamine	urea	amido-acids
carbamic acid	diamido-acids	allantoin	hippuric acid
cyanide	ptomaine	oxaluric acid	taurin derivative
uric acid purin bodies creatinin albumin, albumoses nucleo-proteides		(creatinin)	cystin derivative (leucin, tyrosin, etc.) oxyproteic acid.

We can distinguish from the above—

(a) The easily split off N of the precipitate = "ammonia fraction."
(b) ,, difficultly ,, ,, ,, = "diamino-acids fraction."
(c) ,, easily ,, ,, filtrate = "urea fraction."
(d) ,, difficultly ,, ,, ,, = "amido-acid fraction."

If one deducts the nitrogen of the ammonia and purin bodies from the nitrogen of the precipitate $(a+b)$, a very small residue is obtained. Further, only a small percentage of the nitrogen in the normal urine belongs to the nitrogen of the so-called "amido-acid fraction." By means of this method—

	N of Precipitate. *Easy to split off.* Per Cent.	*N of Precipitate.* *Difficult to split off.* Per Cent.	*N of Filtrate.* *Easy to split off.* Per Cent.	*N of Filtrate.* *Difficult to split off.* Per Cent.
Pfaundler	8·3	6·7	78·2	4·8
Krüger-Schmidt	(?)	(?)	71 to 77	3 to 6
Landauer	6·2		90·9	2·9

V. Noorden calculates the following figures from the results of previous analyses :

84 to 87	per cent. of N	in urea.
2 ,, 5	,, ,,	in ammonia.
1 ,, 3	,, ,,	in uric acid.
7 .. 10	.. ,,	in residue.

One ought really to allow a wider range for the urea. From these estimations, one concludes that the urea forms the greater part of the total nitrogen in normal urine, and also, according to Jaksch, in pathological urine. The conditions under which its amount sinks in favour of the ammonia or the uric acid have been sufficiently discussed in the chapters dealing with these. In disease (typhus, diabetes, diseases of the liver) the nitrogen of the amido-acids fraction may be increased [v. Jaksch]. From this the single amido-acids have been successfully determined in gout by means of new methods, most recently those of Ignatowski, etc. (1).

The portions of the tungstic precipitate whose nitrogen is difficult to split off are rarely increased, neither in health nor in disease; pure diamines appear in the urine only in very special instances.

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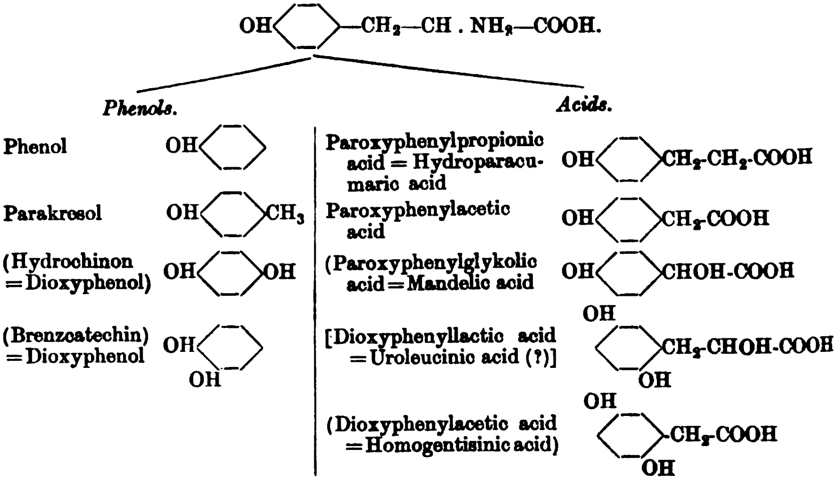
(*h*) Aromatic Group.

Of the aromatic radicals of albumin, which constitute 5 per cent. and more of its substance, single derivatives appear regularly in the urine in small amount, the main proportion being oxidized. The aromatic radical is thus combustible in the animal body, although with greater difficulty than the substances of the fat series. Directly administered tyrosin [Boas, Blendermann], phenyl-amido-propionic acid [Schotten], inosite [Külz], etc., are metabolized, except for slight traces. Of phthalic acid Juvalta recovered 29.5 per cent. in the fæces, and 12·9 per cent. in the urine of the dog.[1] The great proportion must have been consumed, since other aromatic compounds were absent. Indol, if administered, also partly disappears (Jaffé, Wang, Ellinger (2)]. Salicylic acid may be mentioned as an example of a substance which exhibits marked resistance to combustion.

Under normal conditions, the aromatic derivatives of albumin appearing in the excretions are derived from the three different radicals: (1) Tyrosin (phenyl group); (2) phenylalanin (phenyl group); (3) skatolamino-acetic acids (tryptophan, indol group). The following constitution demonstrates the origin from the mother substances:

I. Tyrosin (Paroxyphenylalanin, Paroxyphenyl-amino-propionic acid =Aminohydroparacumaric acid).


OH—CH₂—CH . NH₂—COOH.
Phenols.
Acids.
Phenol
OH
Parakresol
OH CH₃
(Hydrochinon =Dioxyphenol)
OH OH
(Brenzcatechin) =Dioxyphenol
OH OH
Paroxyphenylpropionic acid = Hydroparacumaric acid
OH CH₂-CH₂-COOH
Paroxyphenylacetic acid
OH CH₂-COOH
(Paroxyphenylglykolic acid = Mandelic acid
OH CHOH-COOH
[Dioxyphenyllactic acid = Uroleucinic acid (?)]
OH CH₂-CHOH-COOH OH
(Dioxyphenylacetic acid = Homogentisinic acid)
OH CH₂-COOH OH

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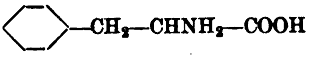
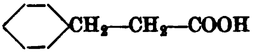
[1] It still remains to be proved whether the glycocoll found by him and by other observers had been present as such in the urine, or whether it had not arisen from the hippuric acid.

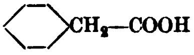
II. **Phenylalanin** (Phenylaminopropionic acid)



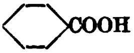
Phenylpropionic acid[1]



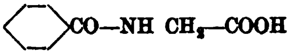
Phenylacetic acid[1]



Phenylcarbonic acid = benzoic acid

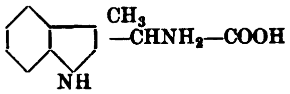


Hippuric acid

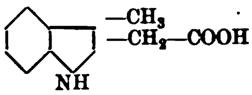


(Dioxyphenylacetic acid.) *Cf.* also Tyrosin.

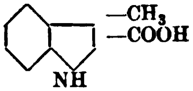
III. **Skatolamino-acetic Acid** (Tryptophan[2])



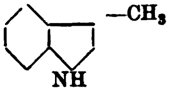
Skatolacetic acid



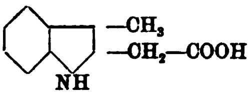
(Skatolcarbonic acid)



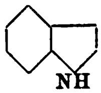
Skatol



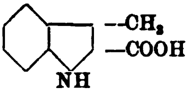
Skatolacetic acid



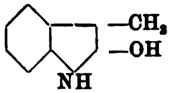
Indol



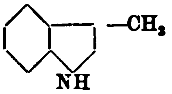
Skatolcarbonic acid



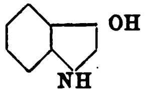
Skatoxyl



Skatol



Indoxyl



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[1] The substances printed in italics are products of putrefaction, and occur only in the intestine or fæces; the others are met with in the urine, generally only in traces (hydrochinon, brenzcatechin, skatolcarbonic acid), or under pathological conditions (as the three aromatic oxy acids).

[2] According to Ellinger, tryptophan is indol-aminoproprionic acid.

A transition of the phenyl group into the members of the phenyl series by means of oxidation cannot be excluded, since in the tissues benzol is oxidized to phenol [Schulzen and Naunyn], and phenol to hydroquinone, and pyrocatechin [Baumann, Preusse, Schmiedeberg (3)]. An oxidation of the aromatic nucleus also takes place in the formation of homogentisinic acid from tyrosin [Baumann] and from phenylalanin [Langstein, Falta], and similar other changes occur.

On the other hand, the transformation of tyrosin into homogentisinic acid which takes place in the human body at least proves the possibility of the reduction of the phenyl group. Another proof of this reduction is the conversion of homogentisinic acid into phenylpropionic acid during putrefaction [Salkowski], although this has only once been successfully demonstrated.

This transition of phenol into the phenol group, however, does not usually occur, and hippuric acid (benzoic acid) is only derived from phenylalanin, and not from tyrosin [Boas, Schotter (4)].

Place of Formation of the Aromatic Sulphates.

The major portion of the above-mentioned bodies was originally found outside the body during the putrefaction of albumin, but they also occur in considerable quantities in the large intestine—as, for instance, phenol and cresol, indol, skatol, and aromatic oxy-acids. Various methods have been employed to determine whether these bodies are formed in the body without the occurrence of decomposition, and if so, to what extent they are present. When putrefaction in the large intestine is inhibited by means of calomel, all these substances, including hippuric acid, disappear from the urine [Baumann]. They are also absent in patients who are suffering from fistulæ of the small intestine [Nencki, Baumann, Ewald, etc.], and also in animals whose intestines have been kept sterile [Nuttall and Thierfelder.] Aromatic oxy-acids found in urine under these conditions therefore originate in the mammalian organism itself, and are not only due to processes of putrefaction. Conditions which increase intestinal decomposition, such as ligaturing of the small intestine and ileum, peritonitis, perityphlitis [Jaffé, Salkowski, and others], lead to an increase of putrefactive products. Outside the intestine, phenol, skatol, and indol are only formed in the course of processes, such as gangrene, bronchiectasis, etc. [Brieger, G. Hoppe-Seyler, and others (6)]. Recently it has been emphatically stated that indol and phenol are formed in the body itself, without the occurrence of any putrefactive processes. Harnack and von der Leyden found such a large secretion of indican in a dog which had been poisoned with oxalic acid that they decided it could not wholly have been formed by intestinal putrefaction. Blumenthal and his pupils, Lewin and Rosenfeld, then performed many experiments, by which they endeavoured to trace back both indol and phenol to decomposing tissue albumin.[1] This latter body has always had to contribute largely to the explanation of any obscure processes. The last two observers discovered that indol and phenol were regularly formed from this body in starved rabbits and in animals which had been poisoned with phloridzin. Ellinger and Scholz disproved these statements, and neither found an increase of indican in dogs poisoned with oxalic acid [Scholz]. Important in the consideration of this question are the experiments of Ellinger and Gentzen upon skatolaminoacetic acid—the substance from which indol is formed. They found that an increase of indican in the urine followed the introduction of this body into the cæcum, where it was decomposed by the bacteria present, and that this increase did not result after subcutaneous injection or after its ingestion. Under the last-named circumstances it was found to become reabsorbed before undergoing putrefaction, this absorption, therefore, taking place in the small intestine (7). So at present the theory that the above-named bodies are formed exclusively in the process of putrefaction must be adhered to.

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[1] *Cf.* "Under-feeding, with regard to the false values of the term 'decomposing tissue albumin.'"

After absorption, the products of putrefaction are in part oxidized. On account of this, skatol and indol are throughout excreted as skatoxyl and indoxyl compounds, and for the same reason phenol is partly converted into hydroquinone and pyrocatechin [Schmiedeberg, Baumann, Preusse, Nencki, Giacosa]. The oxidation of tyrosin into dioxyphenylacetic acid and lactic acid is also exclusively accomplished by the body-tissues [Langstein and Falta], and perhaps also by the formation of oxymandelic acid (8).

Conjugation of the Putrefactive Products.

Of the putrefactive products, the aromatic oxy-acids chiefly appear in the urine as simple salts, the remainder existing in combination with sulphuric acid [Baumann]. The other products of putrefaction combine with other substances in the body tissues: benzoic acid with glycocoll, and the phenols, skatoxyl, and indoxyl, for the greater part, with sulphuric acid, and to a small extent also with glycuronic acid. These paired compounds of glycuronic acid have been thought to exist in normal urine for some time past, and have recently been isolated by Neuberg and Mayer. It has been determined that phenol, indoxyl, and skatoxyl are the bodies with which they unite. Their quantity is, however, far below that of the paired sulphuric acids. It is only when substantial quantities of benzol, phenol, or indol, etc., are given as food that their union with glycuronic acid becomes at all extensive, since the quantity of the existing sulphuric acid is not sufficient for the union of the whole of these bodies [Schmiedeberg (9)].[1]

The figures representing the average daily excretion are as follows:

Phenols: 5 to 30 or more milligrammes per day.
Indoxyl: 5 to 20 or more milligrammes per day.
Aromatic oxy-acids: 1½ to 3 centigrammes per day.

For the latter acids I have personally obtained higher values.

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[1] By this it is, of course, not meant that the union with glycuronic acid only begins when the last molecule of sulphuric acid has been used for combining purposes.

Ethereal Sulphates as an Index of Intestinal Putrefaction.

Since most of these substances are again found in the urine as aromatic sulphuric acids, Baumann estimated the intestinal putrefaction by determining the amount of ethereal sulphates in the urine. This indirect estimation shows that putrefactive products which have been reabsorbed from the intestines are not disintegrated by complete oxidation. This is now also true for phenols, according to Baumann, Preusse, and Schmiedeberg, but the statement is contradicted by Schaffer and Tauber. Indol does not pass through the body entirely unaltered. Jaffé, Wang, and Ellinger found that only 25 to 60 per cent. of the indol which had been taken as food reappeared as indican in the urine. Many valuable conclusions concerning intestinal putrefaction have been arrived at by the above practical method.

In the urine of a healthy individual who is taking a normal amount of food, usually 0·12 to 0·25 gramme of combined sulphuric acid is found. The amount, however, may vary considerably, even if there is no alteration in the quantity of food taken. Thus, von Noorden has found that amounts varying from 0·13 to 0·27 gramme are excreted by the same person during a period of nine days, and by various people on the same diet, quantities of 0·093, 0·12, 0·25, and 0·26 gramme respectively. Similar results have been obtained by Biernatzki. From these variations von Noorden rightly depreciates the importance of small alterations from average amounts, since large quantities after mixed food are associated with an increase in intestinal putrefaction, and so permit but inconclusive deductions.

Von Velden's method of determining the amount of aromatic sulphates as a percentage of the total sulphuric acid has now been abandoned by most authors, since they consider that in this method a wrong view of the matter is taken [Fr. Müller, Kast and Boas, Salkowski, von Noorden (12)]. The quotient ethereal sulphuric acid over total sulphuric acid (usually about $\frac{1}{12}$ to $\frac{1}{15}$) has no value as an indication of the amount of intestinal putrefaction; for the denominator of this fraction, the total sulphuric acid, simply depends upon the total amount of albumin consumed, and has therefore no connection with the putrefaction. A complete replacement of preformed sulphuric acid by combined sulphuric acid very rarely takes place, and then only in experimental poisoning. When the food contains much albumin, and after adding albumin to the ordinary diet, there is usually more ethereal sulphuric acid found in the urine than when the food is poor in albumin. The more albumin present in the intestines, the greater the quantity that falls to the share of the bacteria for decomposition under the same circumstances. An increase in the amount of sulphuric acid after feeding on large quantities of fat was observed by O. Nasse. On feeding with carbohydrates, the amount of sulphuric acid usually decreases greatly [Hirschler, Fr. Müller], and this is also the case with milk, koumiss, and cheese [Biernatzki, Poehl, Rovighi]. When fermentation of carbohydrates in the intestine becomes a predominating feature, there is a diminution in albumin putrefaction. When the food consists exclusively of bread, indoxyl disappears altogether from the urine [Rubner (13)].

According to this, a change in the cultivating medium influencing the putrefaction of albumin by promoting other fermentation is quite a possibility. A direct limitation to intestinal putrefaction in the shape of antiseptics has very little effect in decreasing it. Baumann alone has been successful in reducing the aromatic products in the urine of a starving dog to a minimum by giving it calomel. In a human being no diminution was noticed by Morax, Steiff, and Biernatzki, but Rovighi and Bartoschewitzch noticed a slight increase of ethereal sulphuric acid after administering the same drug (14). It is not the disinfection, but the purging which accompanies it, that decreases putrefaction, by curtailing the stay of fæcal masses in the large intestine. Therefore, uncomplicated diarrhœa and purging by mineral salts tend to prevent putrefaction. With regard to drugs, hydrochloric acid causes a reduction in the amount of ethereal sulphuric acid [Schmitz, Biernatzki], and alkalis cause an increase [Kast and Stadelmann], but these experiments have been the subject of much dispute. Therefore the disinfecting power of the gastric juice is not the only essential factor in determining the extent of putrefaction in the intestine, in a healthy individual [*cf.* Gerhardt (15)].

In starvation there is no cessation of the excretion of putrefactive products. The secretions of the large intestine yield the material for this [Baumann, Salkowski]. More combined sulphuric acid can be excreted by a fasting individual than by one receiving full nourishment [J. Munk]. There is simultaneously an increase in the quantity of phenols [Munk], whereas indican completely disappears from the urine, and indol from the fæces [Fr. Müller]. In the dog phenol is absent [Baumann], but indican is present in large quantities [Fr. Müller and others]. In dieting, there may be noticed many differences in the putrefaction and in the decomposition of the aromatic products. These differences are observed, not only between vegetable and flesh feeders and omnivorous animals, but also in the same individual under different circumstances (16). The putrefactive products which have not been reabsorbed, but which are excreted with the fæces, are, as a rule, not estimated, since they do not enter into the general metabolism, and are thus not harmful. The determination of their amount is desirable in estimating the extent of intestinal putrefaction.

Therefore Baumstark has recently pointed out that the indol of the fæces exceeds in quantity the indican of the urine [C. F. Neubauer (17)].

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(i) Sulphur.

In all researches upon albuminous bodies there has been found but one of the sulphur-containing groups of albumin, this one being cystin (disulphide of cystein = β-thio-α-amido-propionic acid—$CH_2SH\text{-}CHNH_2\text{-}COOH$). Concerning others of these bodies, of those which give rise to the formation of α-thio-lactic acid, nothing is yet known.[1]

Sulphur Combinations in the Tissues.

In the intermediate metabolic processes two sulphur-containing bodies, sulphocyanide and taurin, are present. Both of these bodies have but a limited circulation in the body—the former in the saliva and gastric juice only, the latter combining with the bile-acids, entering the intestine with them, and here being chiefly reabsorbed. The fæces contain only a small amount of sulphur.

Sulphocyanide, whose atomic grouping is not represented in the albumin molecule, is probably formed in the tissues by the synthesis of a sulphur-containing group with a cyan group [Lang (2)]; taurin is derived from cystein. Friedmann (3) has been able to oxidize cystein in a test-tube, and from it thus form taurin. When cystein is administered to a dog or to a rabbit, there is an increase in the quantity of the organic sulphur in the bile and in the liver [Bergmann, Wohlgemuth]. Only a portion of the total quantity of the transformed sulphur appears in the bile as taurin; in the dog about 30 per cent. is normally present [Bidder-Schmidt]. When much meat is taken, the quantity of sulphur in the bile rises, but not proportionately with the quantity of sulphur taken up by the ingested albumin. When eight times more meat than usual is given, only double the usual amount of sulphur is contained in the bile. This increase is only noticed after a considerably greater lapse of time than is normal—*i.e.*, two or three days after it has been given [Spiro, Kunkel].

Even in this there may be observed an independence in the splitting off and excretion of the single constituents of the albuminous molecule, which is not observed after an ordinary mixed diet. A small portion of the sulphur, under these circumstances, is ultimately excreted as the greater part of the excreted nitrogen.

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[1] C. Neuberg and P. Mayer found an α-amido-β-thiopropionic acid in calculus-cystin.

That cystin is a real intermediate metabolic product is not only evident by its relation to taurin, but also by the fact of its occurrence (which is, however, rare) in the urine of human beings (cystinuria), but it is best proved by the experiments on dogs. Cystin can be made to appear in the urine by the ingestion of halogen-benzol cystin, just as is done in the case of glycocoll by means of benzoic acid. The excretion of mercapturic acid is an experimental cystinuria [Baumann and Preusse Friedmann].

Combinations of Sulphur in the Urine.

Nearly the whole of the sulphur reappears in the urine; when completely oxidized, it occurs as free or combined sulphuric acid, and in organic combination as neutral or organic sulphur. The quantity of the total sulphuric acid, which depends exclusively on the albuminous exchange, is stated as being 1·5 to 3 grammes of SO_3 under average nutritional conditions. Baumann's statement that sulphuric acid, when completely formed, combines with aromatic products to form ethereal sulphuric acid, is contradicted by Tauber. According to the latter, it is a precursor of sulphuric acid—probably sulphurous acid—which enters into the above-mentioned combination. If this is correct, it probably follows that the whole of the sulphuric acid is always oxidized from this intermediate product, since it is possible to cause the absolute disappearance of preformed sulphuric acid by feeding with phenol and benzol (5).

The locality in which the combination takes place has recently been stated by Embden and Glässner to be the liver. The musculature is probably not concerned in the process (6).

The quantity of neutral sulphur in the human being amounts to 14 per cent. to 25 per cent. of the total sulphur (7). On feeding with bread, Heffter observed that the quantity rose to 33 per cent. After muscular work there is a slight increase of the excreted sulphur, but this increase is only noticed in the case of sulphuric acid, and not in neutral sulphur [J. Munk]. In starvation there is both a relative and absolute increase in the amount of neutral sulphur in spite of the diminished exchange of albumin [Fritz Müller, Harnack and Kleine, O. and E. Freund], and this same increase may be noticed in disturbances of the oxidation processes, as in poisoning with chloral hydrate, etc. [Harnack and Kleine]. According to these observers, an incomplete decomposition of sulphur-containing bodies occurs simultaneously with an incomplete oxidation of the nitrogenous constituents, and an increase of neutral sulphur indicates an increase in the urinary nitrogen other than urea (7).

A quantitative division of the neutral sulphur in the urine into the separate combinations which contain sulphur, is at present impossible, since these latter bodies are not yet fully recognised. Part of the sulphur is contained in sulphocyanide, of which the daily quantity rarely reaches as much as 100 milligrammes, and a further portion is contained in derivatives of taurin. When taurin is given as food to a human being it is not oxidized to sulphuric acid, but appears in the urine as tauro-carbamic acid, thus increasing the quantity of neutral sulphur present [Salkowski (9)]. If the bile is caused to be excreted externally, and therefore also the taurin, there is a decrease in the normal amount of sulphur in the urine, but it does not disappear completely [Kunkel, Lépine and Guérin]. If, on the contrary, there is obstruction to the flow of bile (icterus), so that taurocholic acid is excreted directly into the tissues instead of into the intestine, the sulphur in the urine is increased (Lépine and Flavard (9)]. Alsberg states that the administration of cholic acid increases the excretion of neutral sulphur. The increase develops slowly, and is in part due to protein catabolism, which, however, it outlasts.

Uroproteic acid, of which as yet little is known, contains neutral sulphur [Cloetta, Gottlieb and Bondzynsky (10)]. Sulphuretted hydrogen and bodies which resemble cystin, and those which yield a black precipitate with lead and thiosulphuric acid, are never found in human urine. Even in dogs and rabbits cystin does not appear in the urine, either in this condition or as cystein [Goldmann, Bergmann, Wohlgemuth, Blum (10)].

A certain relationship exists between the total nitrogen and the total amount of sulphur excreted, since both these bodies originate from the decomposition of albumin. This relationship is, however, not a constant one, since there is a far greater variation in the amount of sulphur in the various albuminous bodies than in that in the nitrogen, the quantity in the former varying from 0·8 per cent. to 2·0 per cent., and in the latter from 15 per cent. to 17 per cent. The comparison is, however, easy under the same feeding conditions [Bischoff and Voit, Sherman], and it has been determined that for every gramme of sulphur about 14 to 16 grammes of nitrogen are excreted. If nitrogen is retained, then also sulphur remains inside the body and *vice versa* (11).

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(*k*) Bodies of Doubtful Origin.

(*a*) Oxalic Acid.

Alimentary Oxaluria and the Formation of Oxalic Acid in the Body.

The oxalic acid excreted in the urine is partly derived from the food, in which it occurs in the form of green vegetables, tea, etc., and is partly formed in the body itself. "Alimentary oxaluria," whose existence for a period was doubted, has recently been again demonstrated by Pierallini, Stradomsky, Dunlop (1). How much of the oxalates of the food is reabsorbed partly depends upon gastric conditions. The larger the quantity of acid formed in the stomach or introduced into it, the more oxalic acid there appears in the urine [Dunlop, Mohr and Salomon, Klemperer]. In a case of achylia there was no trace of oxalic acid in the urine although spinach was taken as food, but it immediately reappeared upon giving hydrochloric acid [M. Rosenfeld (2)]. The amount of oxalic acid is reduced by taking alkalis [Fürbringer, Mohr and Salomon, Hildebrand (3)]. It is, however, not certain that oxalic acid in the presence of lime (calcium) is only reabsorbed when there is an acid reaction—that is, in the stomach—as has been understood to be the case by several authors [Minkowski]. Oxalic acid is also formed in the body tissues. It is excreted when the food, practically speaking, is free from oxalic acid,[1] both in the dog and in man [Fürbringer, Mills, Lommel

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[1] Even lean meat and glandular organs contain small quantities of oxalic acid [Salkowski, Cipollina], as also wine, beer and bread [Pierallini (4)].

Lüthje, Mohr and Salomon]. The most convincing proofs are the experiments upon starving dogs, which, after fasting for thirteen to twenty days, still excrete oxalic acid.

The Sources of Oxalic Acid.

The determination of the mother-substances from which oxalic acid is formed has not yet been successful. The simple nature of the substance allows of a relation between it and all food-stuff, as its formation in the laboratory from all manner of substances serves to show. Under normal conditions traces up to 20 milligrammes appear in the human urine daily,[1] and the increase on introducing various substances is so little (it amounts to from 5 to 10 milligrammes; seldom more than 20 milligrammes) that it is difficult to say with certainty that these minimal quantities of oxalic acid are the end-products of food-stuffs introduced in quantities from 50 to over 100 grammes.

Experiments on the dieting of animals have given the following result: addition of carbohydrate or fat, preceded by flesh or mixed food, or after a period of fasting, diminishes the amount of oxalic acid [Mills, Lüthje, Stradomsky (6)]. Oxalic acid does not, therefore, owe its origin in the body to fats or carbohydrates (*vide* the results of Mayer and Hildebrand).

In the case of dogs, Mills (7) has found that the amount of oxalic acid is highest on a diet of flesh alone, and Stradomsky finds the values for the human being on flesh food higher than those on continued carbohydrate or fat dietaries. There does not, however, appear to exist a parallelism between nitrogen and oxalic acid excreted [Lommel]; addition to food of pure protein, such as plasmon or eukasin, produces a quicker reduction in the amount of oxalic acid separated [Salkowski, Stradomsky]. Connective tissue, on the other hand, increases the amount of oxalic acid excreted; Lommel, Mohr and Salomon, and Stradomsky find an increase of 10 to 20 milligrammes brought about by 40 grammes of gelatin. Klemperer refers the presence of oxalic acid to the glycocoll contained in gelatin, but the increase in the amount of the acid in the human urine after administering glycocoll is so small and so remarkable in the case of a dog after a single subcutaneous injection of ½ gramme of glycocoll (the amount of acid remained the same for twenty-three days) that one must first await further experiments (7).

Since the time of Woehler and Frerichs uric acid has probably been regarded by many as the mother-substance of oxalic acid, on account of its behaviour towards oxidizing agents in test-tube experiments. Neubauer, Gallois and Fürbringer, however, have frequently failed to observe an increase in the amount of oxalic acid after administration of uric acid, and Klemperer has never found any increase at all due to the presence of this substance (8). Feeding on uric acid precursors, such as nuclein, in form of thymus gland or pancreas, did not give positive results. Lommel, Mohr and Salomon found that the administration of calves' sweetbread increased the quantity of oxalic acid slightly, but Lüthje and Stradomsky have not been able to confirm this. Allantoin, also, is not transformed into oxalic acid [Minkowski (8)]. Creatin, which was suggested by Kühne as the possible source of oxalic acid, has not, however, been shown to be so by the later experiments of Stradomsky and Klemperer. The presence of oxalic acid cannot be referred to an aromatic complex such as phenol [Auerbach (9)].

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[1] Stradomsky has found as much as 8 milligrammes oxalic acid in the fæces per diem. Many of the older results are doubtful on account of insufficient analytical methods. The new methods of Salkowski and Autenrieth are reliable, however. The first pays regard to the oxaluric acid also.

One cannot even infer that the slight increase in the amount of oxalic acid always excreted after administration of gelatin is really due to the presence of this substance or its components (glycocoll). It would appear as if the formation of oxalic acid in the body was a secondary reaction due, perhaps, to local disturbance during oxidation processes (*vide infra*). Certain authors have stated, in fact, that a deficiency in the oxygen intake produces an increased separation of oxalic acid [Reale and Boeri, v. Terray (10)].

Difficulty in the Combustion of Oxalic Acid.

It can by no means be assumed that this acid occurs regularly in large quantities during the intermediate processes of metabolism, and is then further decomposed, in the sense that one can call it an essential secondary product of metabolism and place oxaluria on a parallel with cystinuria and diabetes. The combustion of oxalic acid is much too difficult for that.

Certain authors—for example, Gaglio, and in particular Pohl—hold that oxalic acid is quite incombustible in the body. The latter arrived at this conclusion from the results of a single, though no doubt exceptionally well-worked-out, experiment. Lommel, Marfori, Stradomsky and Klemperer, on the other hand, found that only 30 to 40 per cent. of the oxalic acid administered reappeared in the human urine and fæces. It is quite possible that the missing 60 to 70 per cent. was decomposed in the intestine, for oxalic acid disappears by putrefaction [Stradomsky, Klemperer]. Moreover, Hildebrand found that only part of the oxalic acid which he injected subcutaneously into a rabbit appeared again in the urine (11).

Further Relations of Oxalic Acid.

Of the substances which are not usually present in our diet, ethylene-glycol has been shown to be a precursor of oxalic acid. Its direct transformation into oxalic acid has been fully confirmed [Pohl, Paul Mayer], although its origin in the body can hardly be admitted. Ordinary alcohol and the various acids of the series C_2 to C_4 do not form oxalic acid (mono- and di-carboxylic acids, hydroxy and keto acids have been examined [Marfori, Pohl]). Only recently has it been discovered that the administration of dextrose [Paul Mayer, Hildebrand], glycuronic acid, or saccharic acid [Mayer] increases the amount of oxalic acid. This increase, which is quite considerable in comparison with the trifling differences produced by other means, amounts to 10 to 100 milligrammes in the case of rabbits (12). Large quantities of the substances were, however, given to each animal—10 to 20 grammes of the hydroxy acids, and 30 grammes of dextrose per kilogramme. The animals were mostly killed by this "poison" [Hildebrand describes it as oxalic-acid poisoning]. One must, therefore, regard the formation of oxalic acid as the result of the insufficient combustion of the huge doses of these substances administered rather than as a normal decomposition of [a part of] the carbohydrates. Paul Mayer considers it probable that the oxalic acid in his experiments originates from carbohydrates. He found a slight increase in oxalic acid by the autolysis of the liver of rabbits with glycuronic acid, but a similar increase has been observed by Cipollina (13) in digesting liver, spleen, and muscle with uric acid. It is hardly permissible, therefore, to regard the carbohydrates as the only substances from which oxalic acid can be produced to any extent in the body (*vide supra*).

Not the tissues alone, but even the blood, would appear to have the power of forming oxalic acid from uric acid [Garrod, Klemperer (14)], and also of rapidly destroying it. Both statements, however, require thorough reinvestigation and proof.

Whereas many physiological changes have been explained to a great extent by the study of the quantitative increase of given substances under diseased conditions of the body, nevertheless this, unfortunately, cannot be said of the oxalic acid excretion. Here the results obtained are as contradictory as are those which have been observed to occur in the normal human being. I refer to the chapter on oxaluria.

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ADDENDUM BY A. RENDLE SHORT, B.Sc., M.D., B.S.

The majority of the conclusions of the various writers on oxalic acid metabolism depend on their methods of quantitative estimation. It is very doubtful if any are yet even moderately reliable. Those chiefly used are:

Neubauer's, which is criticised by Dunlop, who finds it gives very variable results, often unaccountably high.

Dunlop's, also used by Dr. Helen Baldwin, who seeks to establish its accuracy by adding to a known quantity of urine, in a sample of which the oxalate has been estimated by this method, a known weight of oxalic acid, estimating, and seeing if the acid found, over and above that previously present, corresponds with the amount added. The results are fairly good, but—and Dunlop applies the same objection to Neubauer's method—should some other substance be estimated with the oxalate, this will again appear; and, *vice versa*, should some of the oxalate not come down, a definite quantity being held by some substance in solution, this again will be missing.

Thus, if originally 20 milligrammes are found, of which 15 milligrammes are some substance x and 5 milligrammes oxalic acid, and then 50 milligrammes are added, and 70 milligrammes found, that does not prove that 20 milligrammes were originally present.

There are certain objections to Dunlop's method. It is impossible to accurately weigh calcium oxalate as calcium oxide after ignition, because—

1. The reduction is exceedingly difficult to complete. There is usually some admixture of calcium carbonate.
2. Calcium oxide rapidly takes up water, and is weighed as calcium hydrate.
3. It is impossible to get rid of all the calcium phosphate.

Salkowski's and Autenrieth's Method.—Of this I have no experience.

O. C. M. Davis and I have attempted to amend Dunlop's method by titrating the washed calcium oxalate crystals precipitated by alcohol against potassium permanganate in dilute sulphuric acid, but we do not claim any greater accuracy, as there is still some oxalate shown by this method when no crystals of calcium oxalate can be obtained after adding alcohol to the urine and allowing to stand.

However, the results have a certain relative value, though probably all are too high. Our results show:

(*a*) The average excretion of oxalic acid is about 12 to 15 milligrammes per diem (mean of twenty observations).

(*b*) The excretion very accurately parallels the ingestion of oxalates in the food. Thus, after taking 4 ounces of fruit salad and 3 ounces of rhubarb on March 12, my daily excretion on March 13 reached 48 milligrammes, associated with a copious deposit of large oxalates and scalding pain on micturition. On another occasion 2 ounces of rhubarb raised the excretion to 27 milligrammes. A case of oxalic acid poisoning yielded 146 milligrammes. On the other hand, on a diet of milk and beef-tea, three patients showed no oxalate crystals at all on standing the urine with alcohol.

(*c*) The metabolic diseases do not alter the oxalate excretion. Thus, in diabetes, representing carbohydrate and protein katabolism, there were in two cases (one of whom died of coma two days after) 13 and 16 milligrammes respectively on ordinary hospital diet; in another, on restricted diet, however, it rose to 22 milligrammes. In two cases of leuchæmia, as representing the katabolism of purin bodies, the oxalate excretion was respectively 11 and 4 milligrammes. In fevers there is a great reduction, due to the low diet.

(*d*) In ten cases in which both oxalates and phosphates were estimated, there was no relation between the amount of the latter and the spontaneous deposition of oxalate of lime crystals. I doubt, therefore, if it is the most important solvent.

(*e*) Oxalate crystals dissolve in decomposing urine.

In the absence, therefore, of any reliable method of estimation, and seeing how closely the ingestion and excretion curves follow one another; considering the absence of oxalate crystals in the urine, after standing with spirit, of cases on milk diet (Dunlop, Baldwin, Rendle Short); the failure of numerous observers to prove that any special constituent of the animal body yields oxalic acid; and finding that in diabetes, leuchæmia, and fevers it is not increased, I doubt the formation of oxalates in the normal body.

Miss Helen Baldwin found that the daily excretion of oxalic acid fluctuated with the amount of food, and varied from 2 to 23 milligrammes, the average being 10 milligrammes. She has shown, however, that in dogs rendered dyspeptic with much sugar oxaluria can be produced on an oxalate-free diet. She has observed such cases also in men. This is due to absence of the gastric juice, and consequent fermentation of the carbohydrates in the alimentary canal, producing oxalic acid, which is absorbed and excreted. The gastric contents contain oxalates, and will ferment sugar, with production of oxalates (15). *Mayer* and *Hildebrand* obtain similar results.

Cases of gastric dilatation and achylia do not in my experience develop oxaluria, nor are there oxalates in the stomach. Perhaps they would be present were such patients fed copiously on sugar.

(For further discussion, see section on Oxaluria in Vol. III.)

(*b*) VOLATILE FATTY ACIDS.

The Lower Fatty Acids.

What has already been said regarding the origin of oxalic acid is also true of the fatty acids. From a purely chemical standpoint they can be regarded as derivatives of protein quite as well as of carbohydrates and fats. Indeed, they are products of the fermentation of carbohydrates, and are likewise produced in great quantity by the putrefaction of protein; they also result from the decomposition of fats by bacteria.

About 60 milligrammes of these lower fatty acids, calculated for acetic acid, are excreted in the human urine daily [Rokitansky, Magnus-Levy]. The lower values given by v. Jaksch would appear to be due to the insufficiency of his methods. Blumenthal, Strauss and Philippsohn, and also Rosenfeld, give still higher values (40 to 80 c.c. deci-normal acid, equivalent to 240 to 480 milligrammes acetic acid) (1). The greater quantity consists of acetic acid along with much smaller quantities of formic acid and butyric acid. The presence of propionic acid [Salkowski] is not yet sufficiently determined. Acids with a greater number of carbon atoms are not excreted in the human urine to the same extent as in that of herbivorous animals. Nevertheless, very small quantities of solid fatty acids have been identified by Mörner and Hybbinette (2).

The formation of these volatile fatty acids takes place in the intestine, where they are produced in the lower as well as in the upper portion largely by fermentation [Macfadyen, Nencki, Sieber, A. Schmidt (3)] of the carbohydrates. Food-stuffs, such as meal, increase the quantity of volatile acid in the urine ten times [Rokitansky], whereas no increase has been observed from the administration of dextrose or white bread to other foods [Strauss and Philippsohn, Fr. Rosenfeld (4)]. On a diet of bread alone the amount of these acids is high (equivalent to more than 8 c.c. of normal alkali [Rubner]. Blumenthal states that an increase in their amount is produced by the administration of large quantities of milk. Methyl alcohol is transformed into formic acid, but ethyl alcohol is not [Pohl (4)].

The greater part of the acids absorbed from the intestine is burnt in the body. Schotten found that the amount of volatile fatty acid in the urine of horses was not increased much by administration of caproic acid, valerianic acid, or normal and iso-butyric acids, and similarly Strauss, Philippsohn and Rosenfeld did not find much increase in the human urine after 20 grammes of the sodium salt of butyric acid. On the other hand, acetic acid, and in particular formic acid, are much more stable in the organism, in agreement with the observation that the volatile fatty acid in normal urine consists largely of acetic and formic acids [Schotten, Gréhant and Quinquand (5)].

It is probable, however, that volatile fatty acids are produced in the organism itself. Von Jaksch (6), who has found an increase in fatty acids in certain diseases produced by derangement of the liver, deduces, although without conclusive evidence, that this increase is produced by the decomposition of protein in the tissues [Magnus-Levy (6)]. The author refers the origin of the substances found here (formic, acetic, butyric, and probably caproic acids) to a fermentation of sugar. Conclusive evidence is still wanting of the most probable origin in the body of the volatile fatty acids excreted in the urine which are not produced by the aid of bacteria.

One can take it for granted that it is in the milk-glands of ruminating animals where the formation of these substances takes place. It only remains to be pointed out that butyric acid administered to bitches does not pass into the milk [N. Zuntz], whereas the higher fats not belonging to the body—as, for example, iodipin—appear again in the milk after feeding [Winternitz (7)].

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(c) Cholesterin and the Bile Acids.

The origin and the significance of this substance are quite unknown. It is an essential constituent of every cell. Whether it is formed in the animal body, or only passes from the vegetable kingdom into the animal organism [Bunge], is still uncertain.

The cholesterin which is taken into the body in food appears again unaltered or in reduced form as coprosterin in the fæces. It is practically absent in the urine.

Its occurrence in the bile and its relation to gall-stones are subjects which have given rise to a great deal of investigation in the laboratory of Naunyn. Cholesterin administered *per os*, or injected subcutaneously, does not increase the quantity of cholesterin in the bile [Jankau]. No relation has been found between the amount of cholesterin and the nature of the food supplied to the body, although it has been shown that the amount of fat in the bile can be doubled by dieting on fat [Thomas]. The most varied diseases (with the exception of cholelithiasis) produce no effect on the amount of cholesterin in the bile. Naunyn therefore holds that the cholesterin does not arise from the hepatic cells proper, but from the cells lining the bile-ducts, and in particular the gall-bladder. Stadelmann considers that a circulation of cholesterin into the intestine and back into the tissues does not exist.

Cholalic Acid.

The origin of cholalic acid, like that of cholesterin, is at present quite undetermined. Its relationship with cholesterin is, however, possible, judging from its composition and staining reactions. The liver is its exclusive seat of formation. It is entirely absent in a frog from which the liver has been removed [Köbner], and similarly from dogs in which the bile-duct and thoracic duct are simultaneously ligatured [Ludwig and Fleischl (1)].

In contradistinction to bilirubin and cholesterin, a definite circulation has been completely proved in the case of the bile acids. These acids are discharged into the intestine. Their amount Stadelmann (2) accepts as 10 grammes, although on uncertain grounds. Of this amount—

1. A certain proportion appears, either changed or unchanged, in the fæces (up to 30 to 40 per cent.).

2. Traces (a milligramme) occur in the normal urine [Naunyn, Vogel, Höhne, Dragendorf (3)].

3. A very large proportion (50 to 80 per cent.) is reabsorbed from the intestine, and again secreted by the bile. This fact has been ascertained from experiments on animals with complete biliary fistulæ. In these otherwise healthy animals the amount of the acids excreted from the liver gradually diminishes [Bidder and Schmidt, Schiff, Stadelmann (4)]. If, however, the animals be given bile acids in the food, these appear almost measure for measure in the bile from the fistula (Schiff, Weiss, Stadelmann (5)]. Indeed, the combined bile acids seem to become reabsorbed as such, partly, at least, without previous cleavage, since after feeding dogs with pig or ox bile (which contains glycocoll) glycocholic acid makes its appearance in the bile of these animals (this substance being commonly absent, or present only in minute quantities) [Weiss, Stadelmann (5)].

Thus, the amount of cholalic acid freshly formed in the body every day is only a trace compared to that circulating daily in the bile, and is probably not more than the quantity lost in the urine and fæces [Kunkel]. After their reabsorption the bile acids pass, partly at least, through the lacteals. Tappeiner (6) has detected them in the thoracic duct. They are also traceable in minute quantities in the blood, from which Croftan (6) has obtained them in the crystalline form.

4. They appear in the tissues only in pathological conditions.

5. It has not been directly determined whether part of the bile acid is decomposed in the intestines or in the tissues; still, one must at least accept the latter site, since in complete blocking of the bile-duct proportionally small quantities still appear in the urine.

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B.—FATE OF CARBOHYDRATE IN THE BODY.

The carbohydrate of the food is absorbed chiefly as grape-sugar (and maltose ?), in addition to which small quantities of fruit sugar and galactose (originating from cane-sugar and milk-sugar) come into consideration. As soon as the sugar has entered the tissues it can serve various purposes: (1) It undergoes combustion; (2) it may be stored up as glycogen or fat; (3) it may be partly unconsumed and leave the body by the urine.

1. Immediate Combustion of Sugar.

Sugar serves principally for the immediate supply of the needs of the body. That a combustion begins soon after absorption may be determined in a striking manner by a study of the respiration. The respiratory quotient, which in the fasting condition reaches at the most 0·7 to 0·8, chiefly from oxidation of albumin and fat, rises very quickly to 0·9 and 0·95 after the administration of specially dissolved carbohydrate, and with very large quantities of sugar up to 1·0 and over [Zuntz and Mering, Magnus-Levy, and others]. Thus, for example, after 155 grammes of cane-sugar the respiratory quotient rises from 0·77 to 1·01, 0·89, 0·89, 0·92, 0·82, 0·82, 0·79 in the succeeding seven hours [Magnus-Levy] (1).

2. Deposition as Glycogen.

If the absorption of sugar oversteps the immediate requirements, the quantity of sugar in the blood and tissues does not perceptibly increase, the temporary surplus being definitely stored up as reserve material in the form of glycogen, chiefly in the liver and in muscle. By appropriate maximal feeding the quantity of glycogen in the liver can be readily increased 10 per cent. and more; 12 and 15 per cent. [myself], 17 per cent. [Pavy], and 18 per cent. [Schöndorff in the dog] have been observed. Further, the above organs, with maximal supply, can take up glycogen so freely that the glycogen compared with the total weight of the body may rise in extreme cases to 3·6 (= 4 per cent. of sugar) [Schöndorff]. As direct or actual glycogen-formers [Cremer], whose carbon is *transformed* into glycogen, the following have been recognised, chiefly from the comprehensive experiments of the Voit school: grape-sugar and fruit-sugar, and also—though in smaller proportion—galactose; so also the carbohydrate element in every class of sugar, starch, maltose, isomaltose, and also cane- and milk-sugar, though in feebler manner [Karl Voit, Cremer, Kausch and Socin, Weinland, and others (3)]. These all give rise to liver glycogen freely when introduced into the bowel; fruit- and grape-sugar also by subcutaneous injection [Karl Voit and his school].

A simple anhydration is alone requisite for the transformation of grape-sugar into glycogen. Fructose and glucose are thereby apparently first transformed into grape-sugar, for glycogen, from whatever source it arises, contains only grape-sugar in its molecule, and no other kind of sugar. Experiments with diabetics and the phloridzinized animal show that a conversion of fructose, etc., into grape-sugar can readily take place. Of 100 grammes of galactose, 70 per cent. reappears in the urine of diabetics as grape-sugar [Fritz Voit]. Minkowski found in an animal with its pancreas removed that lævulose given by the mouth was excreted for the greater part as grape-sugar (4). The transforming of fructose into glucose in the animal body, the chemistry of which was previously known only in a circumstantial manner [Emil Fischer], has lost a part of its mystery, since Lobry de Brun and Eckenstein (5) have shown that the action of quite weak alkalis suffices to change glucose, mannose, and fructose into one another. The transformation of fruit-sugar into grape-sugar occurs chiefly in the liver, according to Strauss. In liver disease the utilization of lævulose is especially imperfect (5). The same is seen in frogs after liver extirpation [H. Sachs (5)]. Whether all the fructose, as also that which undergoes direct combustion, is previously transformed into glucose is as yet not decided. It is probable, from recent experiments on lævulosuria, that in rare instances invert grape-sugar is transformed into fruit-sugar.

3. Transformation into Fat.

By maintaining an excessive supply of carbohydrate the store of glycogen will be so complete that additional carbohydrate cannot be further assimilated. The maximal amount of glycogen in the body from excessive feeding (see also Schöndorff's researches above) rarely exceeds 1 to 2 per cent. of the body-weight. For the human subject Neumeister (6) accepts the possibility of a storing up of 300 grammes of glycogen; still, the maximum in an adult of 70 kilogrammes may reach higher amounts n some cases.[1] The storehouse for glycogen being filled to a certain tandard,[1] then additional carbohydrate will be changed into fat and tored up as such, if the continued absorption exceeds the using up.

Carbohydrate is, next to fat, the most powerful fat producer. The ngenious Brillat-Savarin ascertained this one hundred years ago from daily observation. The products of practical husbandry point emphatically to this transformation. And yet this idea, which Liebig accepted, fell into oblivion when Pettenkofer and Voit advanced the view that albumin was the main source of the body fat. Researches on dogs, pigs, sheep, and geese during the eighties of the last century have raised the question of the transformation of carbohydrate into fat to a certainty. All these researches (7) have this in common: that the animals, after more or less prolonged partial inanition, were supplied with food freed as much as possible from fat and albumin, but unusually rich in carbohydrate. The determination of fat formation in the animals was made either directly or indirectly. In some cases the animals, having become deficient in fat during the preliminary experimental period, were killed after prolonged carbohydrate feeding, and the increase of their body fat analytically determined (from comparison with the amount of fat in a control animal). There was much more fat deposited than could have been derived from the fat of the food and the albumin during the whole feeding period. The excess could only arise from carbohydrate. In other cases [Meissl, Rubner] the proof was obtained from observations on the respiration during twenty-four hours. From the comparison between the carbon excreted in the expired air and in the urine with that absorbed from the food the result was that vast quantities of carbon, derived from carbohydrate, were being retained in the body. These could be stored only as fat, since the glycogen depots during the preceding days were already filled to the maximum. I can furnish only one example to show to what extent this fat formation can take place from starch. Meissl (7A) fed a pig of 71 kilogrammes with 2 kilogrammes of rice daily, and found therefrom a daily deposit of 409·5 grammes of fat, of which, allowing for the difficulty of calculation, at least 363·8 grammes must have been formed from carbohydrates. About one-half of the starch in the food (1575 grammes) was retained in the body as fat. The transformation of carbohydrate into fats is thus a definitely-ascertained fact, which is now applied extensively in therapeutics (7).

This transformation into fat takes place perceptibly, being permanent only if the supply of carbohydrate greatly exceeds the needs of the tissues. However, Hanriot and Richet (8), from respiratory experiments, have concluded that, even with supplies which are not excessive, at least part of the carbohydrate is changed into fat. Still, Magnus-Levy has pointed out that the experimental evidence for the conclusions of these authors is not accurate. There are no grounds, therefore, for believing that readily-combustible carbohydrate, which plays the chief part in the nutriment of plant-eating animals and omnivorous man, must be first of all transformed into fat in order to undergo combustion as such.

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[1] The formation of fat is certainly already begun before the absolute feeding maximum is reached.

In diabetes, von Noorden readily accepts the possibility of a constant change of the sugar into fat, and believes that certain diabetics possess the capacity of burning off their sugar by first transforming it into fat. Naunyn also favours the possibility of this proceeding (9).

The formation of fat from carbohydrate is also highly interesting theoretically as a process of synthesis and reduction, which in its importance leaves far behind it all similar changes in the animal body. Starch and grape-sugar possess a much greater amount of oxygen than fats, and this excess of oxygen must become separated during the transformation (reduction).

		C.	*H.*	*O.*
		Per Cent.	Per Cent.	Per Cent.
100 grammes sugar ..	=	40·0	6·7	53·3
100 „ fat ..	=	76·5	11·9	11·6
191·3 „ sugar ..	=	76·5	12·7	102·05
In 191·3 grammes sugar ..		—	0·8	90·4 more.

During this transformation it is improbable, from a chemical standpoint, that the excess of oxygen is split off from the carbohydrate molecule as such, and then serves for the oxidation of albumin, fat, or other carbohydrate molecules [Liebig, Hoppe-Seyler, Pflüger, Bleibtreu, Magnus-Levy (10)]. More accurate is the view that (just as in the case of butyric acid and alcoholic fermentation) a part of the sugar carbon (saturated with oxygen) passes out of the sugar molecule as CO_2, while the remaining carbon compounds, being now poorer in oxygen, combine to form higher fatty acids. The change may be effected somewhat as follows, accepting the view of Hoppe-Seyler, which has been adopted by Magnus-Levy:

$$\text{I.}\left\{\begin{array}{l} \underset{\text{Grape-sugar.}}{9C_6H_{12}O_6} = \underset{\text{Lactic acid.}}{18C_3H_6O_3} = 18CO_2 + 18C_2H_4O + 18H_2. \\ \hline 18C_2H_4O + 14H_2 = \underset{\text{Stearic acid.}}{2C_{18}H_{36}O_2} + 14H_2O. \end{array}\right.$$

In the case of oleic and palmitic acids the formula requires slight modification. The glycerin necessary for the synthesis of neutral fat in the body is at all times readily supplied (see the chapter on Digestion of Fat). Perhaps this glycerin also arises from sugar.

This view supports the following empirical equation of Bleibtreu:

$$\text{II.}\left\{\begin{array}{l} 270{\cdot}06 \text{ grammes grape-sugar} = 100 \text{ grammes swine fat} \\ \qquad + 54{\cdot}61\ H_2O + 115{\cdot}45\ CO_2. \end{array}\right.$$

This formula, which will at all events need subsequent modification, yet gives an idea of the maximum amount of fat which can originate from grape-sugar. Accordingly, 100 grammes of grape-sugar ought to yield 37 grammes of fat. If concomitant reactions of other kinds take place, which is not improbable, then the amount of fat would be less. Besides, the reaction is an exothermal one. It takes place with a slight production of heat: 37 grammes fat represent only 37 × 9·5 (or 9·43) = 3,530 (or 3,503) calories, while, on the other hand, 100 grammes of grape-sugar represent 3,692 calories.

The essential feature in this change is, according to the hypothesis of Equation I., on the one hand, the splitting off of CO_2 and the formation of carbon compounds poor in oxygen (with two atoms of carbon, like acetanilid [Nencki]), and, on the other hand, the synthesis of the latter to form fatty acids. This change has thus a great resemblance to butyric-acid fermentation, which is so widespread in nature [Liebig]. Still, it ought to be expressly emphasized that this explanation is as yet only a hypothesis, which has not yet been proved. However, according to Rosenfeld (confirmed by Röhmann), during fattening with carbohydrate it is pre-eminently the stable glycerides of fatty acids which are formed, along with a little tri-olein; so that "carbohydrate fat" is fairly stable, and melts early with higher temperatures, like the ordinary fat of the same animals (10).

No certainty exists regarding the site of this change. Liebig considers the liver to be the main centre for this transformation essentially on the ground of the marked fermentation (butyric-acid fermentation) and reduction processes which occur in the liver after death. Magnus-Levy also supports this view. Rosenfeld is of another opinion. He has traced the various steps of fat storage in the different main "fat depots" during carbohydrate fattening, and noticed that the liver was involved only after the other storehouses were full. He shows, further, that, according to Bleibtreu, the blood of geese so fattened, with the exclusion of all fat in the food, is very poor in fat, and also that no continuous stream of fat passes in the blood from the liver to the subcutaneous tissues. He believes, therefore, that the change into fat occurs mainly in the site of permanent storage, probably in the cells of the subcutaneous tissue (11).

4. Excretion of Sugar in the Urine.

When large quantities of carbohydrate are ingested, a proportion is neither utilized nor burnt off, and so appears in the urine. The amount of carbohydrate which leads to "alimentary sugar excretion" varies according to the type of the carbohydrate and to the individuality of the person (or the kind of animal). Starch in the very largest doses (308 grammes) does not give rise to glycosuria [Miura (12)], or only to a minimal extent (with 260 and 600 grammes [Moritz]). According to Naunyn, a glycosuria *ex amylo* is a certain symptom of an apparent or latent diabetes. Excretion of sugar by the urine is most persistent with maltose, grape-, fruit-, and cane-sugar in doses of from 100 to 150 grammes (also with 200 grammes of glucose) [Moritz, v. Noorden, Strauss, and others]. Milk-sugar, on the other hand, is passed in large quantities by the urine if given in small doses of 50 grammes [Worm-Müller, Moritz], and galactose still more so [see Strauss]. Various authors make different estimations regarding the extent of the limit of assimilation [Hofmeister] or limit of saturation [Fr. Blumenthal], and also judge differently regarding the ease with which the various kinds of sugar are passed by the urine. This is due in great part to the dissimilar reaction of different persons towards the introduction of sugar. Thus, for example, Linossier and Roque observed glycosuria with only 50 grammes of cane-sugar in some individuals, while 350-gramme doses were required in other cases. The other kinds of sugar also possess similar variations. The limit of assimilation of lævulose, whose behaviour is biologically important, is not lower than that for glucose, according to Strauss, who is supported by his own work and by that of Worm-Müller and Fr. Voit; the same obtains in the rabbit [Fr. Blumenthal], although not in the dog [Schlesinger (12)].

The excreted sugar is in most cases similar to that ingested, although after taking milk-sugar grape-sugar occasionally appears in the urine in addition to galactose (?) [Moritz]. So also with cane-sugar, invert sugar often appears in marked quantities in man as well as in animals (the urine being lævo-rotatory). Again, with large doses only a small percentage of the swallowed sugar appears in the urine, especially in a healthy animal, even if the limit of assimilation has been widely overstepped. Thus, Worm-Müller noticed that in the same person 0·1 gramme was excreted after 50 grammes of cane-sugar, and only 0·85 gramme after 150 grammes (12). V. Noorden found—

After giving 100 grammes of grape-sugar, 0·0 in the urine.
" " 150 " " " 0·15 " "
" " 200 " " " 0·26 " "
" " 250 " " " 0·52 " "

Alimentary glycosuria occurs in a healthy person only by saturating the organism with soluble carbohydrate. Therefore it is absent after administering starch, as in this case no more sugar will be absorbed than can be metabolized in the body. It is also scanty, or quite absent, if sugar solutions be given on a full instead of on an empty stomach. Naunyn has observed, regarding alimentary glycosuria, that there is excreted in the urine only that sugar which, according to Ginsberg, reaches the general circulation through the thoracic duct, thus avoiding the liver. His results found support from the researches of Schlesinger and those of Schönborn (13). The former noticed that alimentary glycosuria was absent in the dog after tying the thoracic duct, in spite of the fact that he doubled the doses of sugar which previously had caused glycosuria. Schönborn was only able to produce glycosuria in man by rectal injection of sugar when he limited the absorption to the lowest part of the rectum, since in such cases the sugar would pass through the inferior hæmorrhoidal veins into the vena cava instead of to the liver by the portal vein. Still other external influences may come into play, such as altered capacities of the tissues, especially those of the importantly concerned liver. The result of this may be that excessive doses of glucose are stored up as glycogen or fat in a given time. For saccharosuria and lactosuria the relationships are somewhat different. Here it is very obvious that these double sugars, if given in excessive quantities, are not completely split up in the intestine (or during their passage through the intestinal wall), but enter the general circulation as such. The organism, like most of the yeasts, cannot decompose these sugars to any extent, so that they leave the body with the molecules unaffected. The same result is well known to take place if these kinds of sugar be injected under the skin. In this way quantities of 1 gramme in man have been completely excreted again [Fr. Voit (14)]. (See also lactosuria during suppression of mammary secretion in chapter on Pregnancy.)

5. The Pentoses.

The pentoses (arabinose, xylose, rhamnose) play a small part in the nourishment of man. While plant-eating animals absorb large quantities of them (of 10 grammes, rabbits utilize 80 per cent.)—that is, over 4 grammes per kilogramme [Salkowski (15)]—the conditions in man are much more unfavourable for their combustion. After taking from ½ to 1 gramme of arabinose, xylose, or rhamnose, pentoses are detected in the urine [Ebstein, Cremer]; so also after eating bilberries and other fruits [Blumenthal]. The "limit of assimilation" is thus very low. They act as if the body, as Salkowski says, has a very low "limit of oxidation." By the introduction of large quantities a proportion is always consumed—of 25 grammes of arabinose, about 16 grammes [Cremer and likewise v. Jaksch]. The latter observer noticed that as much as 50 per cent. of the three named pentoses reappeared in the urine if given in doses of 10 to 20 grammes, while rhamnose was also excreted in the fæces. Lindemann and May alone found favourable conditions. Thus, of 99·2 grammes of rhamnose, none passed out in the fæces, and only 7·78 grammes in the urine. The pentoses are thus consumed in the body instead of other materials, and can therefore be sparers of nitrogenous material, glucose, and fat [Lindemann, May, Cremer, disputed by v. Jaksch], and also favourably affect the deposit of glycogen [Salkowski, Cremer, etc.]. They exert the latter effect only by protecting the glycogen produced from other sources, and not owing to the fact that they themselves become transformed into that substance (pseudo-glycogen-formers). (Compare, also, Frentzel (15). For further details, see Neuberg in the chapter on Rarer Derangements of Carbohydrate Metabolism.)

6. Elaboration and Oxidation of Grape-Sugar.

It is not yet known in what manner grape-sugar is oxidized in the body. It is impossible to detect in the blood certain products of decomposition (intermediate stages of the elaboration) in such quantities as to consider them with certainty as derivatives of sugar. We can refer only to the existing possibilities. The sugar may become oxidized without previous splitting, so that the first product to appear is an acid—glycuronic acid (or glyconic acid, sugar acid, or similar products). Paul Mayer (16) has recently produced evidence to show that ordinary sugar is, partly at least, elaborated in this manner. He believes that during metabolism glycuronic acid is formed (appearing frequently in combination with various compounds, or often without the presence of these), and then becomes further oxidized. It is a well-recognised fact that glycuronic acid formed from grape-sugar ordinarily appears in the urine [Neuberg and Mayer] and in the blood [Paul Mayer (16)]. O. Loewi (17) considers that it is always derived from protein, but even if his researches be proved, contrary to our conception, the grape-sugar must always be first formed from the protein, and then glycuronic acid from the grape-sugar. On the other hand, there are no grounds for denying the oxidation of the preformed grape-sugar into glycuronic acid, which the " protein-sugar " ought to become. Paul Mayer and Hildebrandt (17) have produced direct proof for the origin of glycuronic acid from grape-sugar. In a fasting animal, when camphor is administered, it does not all combine with glycuronic acid, since the mother-substance—carbohydrate—is absent. If, however, sugar be given at the same time as the camphor, then the excretion of glycuronic acid rises [Mayer]. Hildebrandt noticed that fatal doses of " thymotinpiperidid " became harmless when he also gave much grape-sugar, so that there was abundant sugar for the formation of glycuronic acid, in combination with which the " piperidid " was no longer poisonous.

There need thus be no doubt regarding the immediate origin of glycuronic acid from glucose. Yet this oxidation is a process which can only take place if certain aromatic products which give rise to the formation of glycuronic acid are circulating in the body. Free glycuronic acid, however, has never been found in the organism or in the excretions. The fact that other substances which generally appear in the urine only in combination are found occasionally in the free, uncombined condition may be considered as proof that they take a regular part in intermediate metabolism (cystin, for example). The existence of a normal elaboration of sugar by way of glycuronic acid [Blumenthal (18) and others] cannot be readily accepted.

The second possibility is that grape-sugar at first breaks down into smaller bodies without oxidation, somewhat after the manner of lactic acid and alcoholic fermentation, and that these smaller molecules undergo the oxidation. It may be recollected that lactose, which is found in the blood and tissues, and often appears in the urine, is formed to a great extent in living organs as well as during autolysis. Still, one must not always exclude its origin from protein in all cases, and thus confirm its origin from carbohydrate alone. Neumeister (19) and others, and more recently Asher and Jackson, have vigorously contended for this point. Magnus-Levy observed that during autolysis of the liver lactose was formed in such quantities that he could determine with a high degree of probability its origin as a decomposition product of sugar. It could not have formed from alanin alone.

Of great significance, if it be confirmed, is the latest discovery of Stocklasa (20), who obtained from plants and also from animal tissues, as several French observers had previously done, an enzyme which, like zymase, produced alcoholic fermentation.

If the metabolism of sugar proceeds in the direction of lactic acid or alcohol, which we think probable, then the decomposition occurs apparently by ferments, just as in autolysis. These have been especially sought for in the pancreatic tissue, as removal of the pancreas arrests the oxidation of sugar either completely or to a considerable extent, but they have not as yet been found there definitely. The liver still appears to have the strongest sugar-splitting action of all single organs [Magnus-Levy (20)]. The glycolytic power of the blood is small [Lépine]. New views have been developed by the work of O. Cohnheim (21). He found that sugar digested in an extract of muscle or pancreas was split only to a small extent, while, on the other hand, an extract from both acted very energetically in this respect. The juice of 100 grammes of muscle digested with pancreatic juice caused 0·5 gramme of sugar to completely disappear in twenty-four hours. Cohnheim has recently published another significant paper, in which he states that a glycolytic ferment is contained in muscle, which needs the presence of pancreas to render it active. Cohnheim succeeded in isolating this agent from the pancreas. It is not affected by heat, and is soluble in alcohol. Thus, it is probably not a ferment, but is rather to be placed on a par with the other earlier known products of internal secretion, such as adrenalin, iodothyrin, and secretin. During glycolysis of muscle (with this pancreatic substance) Cohnheim did not get any distinct production of CO_2 (contrary to Stocklasa). This is against the existence of an alcoholic fermentation. The reaction of the fluid soon became acid. Perhaps this may be lactic acid or a split product of the glycolysis of muscle. Further, the sugar in these researches disappeared by splitting and not by combustion. Cohnheim has not made further communications. Some more of his well-known work will be welcomed with the liveliest interest (21).

Embden and Claus (21) have shown that if the muscle juice be kept free from bacteria, its glycolytic power is not altered by the addition of pancreatic juice.

Reference may also be made to a marked excretion of oxalic acid after administration of large quantities of grape-sugar or glycuronic acid [Paul Mayer, Hildebrandt (22)]. This discovery gives no information regarding the normal elaboration of sugar (see the section on Oxalic Acid).

The observations of Kossa prove that saturation with normal food-stuffs can actually behave as poisons. By subcutaneous injection of cane- and grape-sugar (especially in fowls, and to a lesser extent in dogs and rabbits) he produced the most profound changes, which ultimately lead to death of the animals. The albumin metabolism rose about 50 per cent., instead of the diminution which one would expect after giving sugar. Again, Forster noticed that the excretion of urea rose from 12·5 to 17·9 grammes in a fasting dog after injecting 300 c.c. of a 25 per cent. solution of sugar into a vein. The phosphoric acid in the urine rose at the same time from 1·49 to 2·39 grammes in direct relationship to the urea.

7. The Carbohydrate of the Blood.

The dextrorotatory, reducing, and fermentable substance of the blood has for a long time been considered to be grape-sugar, and this has been confirmed by Pickardt and Miura (23). The sugar is carried in the blood to the organs requiring it, but the amount in the latter is always replenished by withdrawal from the carbohydrate stores or by new formation from protein, so that the percentage of sugar in the blood is maintained at an average level. The reducing power of the blood corresponds to 0·08 to 0·09 per cent. of grape-sugar, according to Naunyn; in the rabbit the figure is higher.

The greater proportion of the sugar consists always of glucose. It has, however, been for long apparent that other reducing substances must be present [Otto (24)]. Bodies such as jecorin have been recently discovered by Drechsel and others. Jecorin is a lecithin containing compound of glucose [Henriques and others]; the latter, according to many authorities, ought to prevail over the free glucose [Kolisch (24)]. Still, the relationships are not convincingly explained, and the above substance has not sufficient chemical characteristics. Further, Paul Mayer (25) found combined lævorotatory glycuronic acid in the blood of cattle. It, however, only represents final excretory products of the body on its way from the active organs to the kidneys. More important is the existence of fructose, the presence of which in the human lymph was first determined by Pickardt (compare also J. Baer (26)]. More recently, Neuberg and Strauss have demonstrated, by means of objection-free methods, that fructose can be found in the blood and effusions of the body cavities in many non-diabetic patients, even when no fructose is taken in the food. Its presence in healthy subjects has not yet been proved. In the blood, glycogen is found not in the plasma, but in the white blood-corpuscles [Huppert, Gabrischewsky, Minkowski (27)]. Cane- and milk-sugar only appear if they are absorbed from the intestine in excessive doses. Lactose also may appear in the blood in women during pregnancy, and also during lactation.

Regarding the origin of carbohydrate (1) from protein and peptones, see the section on protein metabolism; (2) from fats and other substances, see the section on fat.

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C.—FATE OF FATS.

1. The Metabolism of Fats.

After gaining an entrance into the blood-stream with the chyle, the neutral fats remain in the circulation for the brief period which elapses before they are selected by the tissue cells for combustion or storage in the subcutaneous tissue, the paraperitoneal spaces, and the liver. Different ferments have been found to exist in the blood—some in the serum, which split the fat [Hanriot], and others in the red corpuscles,[1] which convert it into the form soluble in water [Connstein and Michaelis, Weigert]. It is admitted that this lipase serves for the passage of the fats from the capillaries into the tissues. The fats ought to be able *to* pass through the capillary wall when split up only, or in a form soluble in water, just as Pflüger considers that they pass through the intestinal wall. B. Fischer (1) goes so far as to refer the extraordinarily well-marked lipæmia in diabetic coma to an absence or a weakening of this ferment.

During the periods of fasting, the fat streams from the depots back again into the blood, in order to supply the organs requiring fat. Here again a previous splitting of the neutral fat is necessary for its passage out of the fat cells into the lymph stream. It thus looks as if the lipase of Hanriot is found also in the liver and elsewhere. In autolytic processes it is often demonstrable how the higher fatty acids become free from neutral fats. During a well-marked retransfer of the fat into the blood the fat contents of the latter are mostly higher than when giving food poor in fat. Such a well-marked "lipæmia" (this expression, as generally employed, is not quite correct, as the blood always contains fat) is found in the fasting condition [F. N. Schulz, Miescher], in phosphorus and phloridzin poisoning [G. Rosenfeldt], in alcoholic intoxication, and in diabetic coma—thus in conditions in which there is more or less widespread inanition, especially with deficiency of carbohydrates (3). But this return stream of fat from the fat depots takes place in much greater proportion, as if it were necessary for the immediate needs of the combustion processes in the body; and this is the most interesting of these changes—at least, in pathological conditions. G. Rosenfeldt (4), in a series of brilliant researches, has shown that, in the above-mentioned conditions, an enormous passage of fat takes place from the depots of the subcutaneous tissue and the abdomen into the liver, the latter thus becoming loaded with enormous quantities of fat (as much as 70 per cent. of its mass). He made use of the methods first employed by Lebedeff and Munk, in which large quantities of foreign fat (mutton or cocoa-butter) are introduced into the body and withdrawn from the liver by several days' fasting. On producing poisoning with phloridzin, alcohol, or phosphorus, he could recognise an enormous increase in the previously normal dog-fat contained in the liver of the dog, and this by analysis could be recognised as mutton-fat.

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[1] The synthesis of fat is described in the section on Digestion.

This storing up of fat in the liver only occurs if the glycogen has disappeared therefrom, and it can be prevented if the animal, during the experiment, be fed with substances from which glycogen is freely formed; thus it will be prevented if much sugar be given (Rosenfeld). The storage of glycogen and fat in the liver thus stand in a certain antithesis, although this is not so absolute as Rosenfeld thinks. I have often found in the livers of crammed Strassburg geese, which I killed shortly after the last cramming, gigantic quantities of fat alongside a very extensive storage of glycogen (4).

All experimental fat storage in the liver allows two explanations: the one, already suggested by Nasse, holds that the liver must first transform the fat molecule in some way before it can be consumed by the cells. According to Chauveau and Seegen (5), the fat is there transformed into carbohydrates (see further below). So long as it is not determined with certainty whether this transformation is facultative or obligatory, then this explanation of the loading of the liver with fat is not convincing.

The second view is that the storage of fat in the liver may also be regarded as an available reserve which must be held in readiness for any sudden call upon the metabolism—as, for example, in violent movements. It is obvious that the finely divided fat can, when necessary, pass more quickly and easily from the extremely vascular liver than out of the drops in the cells of ordinary adipose tissue. According to this explanation, the liver must have the task of placing at the disposal of the body the material necessary for combustion, both from its glycogen and its fat depots, on any sudden increase of the demand.

Other Transportations of Fat.

The recognition of fat by the addition to it of other constituents, in the manner described above, has made it possible also to follow the fat in its other migrations.

For this purpose rape-seed oil, cocoa-fat, sesame-fat, butter, mutton-fat, and, finally, also iodipine, have been utilized, these all being fats which can easily be traced in mixtures on account of their varying chemical behaviour. By these means, not only the disposition in the animal body of fat which has been given as food has been traced, but also its transition into milk [Caspari, Rosenfeld, Winternitz], into the egg of the hen, [Henriques, Hansen, and Zaitschek], and into the coccygeal gland (Röhmann) has been proved.

At the same time, it is interesting to note that, although the fixed fatty acids contained in food are deposited in the body, this is not the case with volatile fatty acids. Leube noticed that these latter were not present in the fat which was deposited in the tissues of a dog after fattening the animal with butter, and neither could Zuntz ascertain that the volatile fatty acids were transmitted into the milk of the dog.

Concerning the oxidation of fatty acids which takes place in animal tissues, the reader is referred to the section dealing with the decomposition of albuminous substances.

The Transformation of Fat into Sugar.

Does a transformation of fat into sugar, such as has been proved to take place in the vegetable kingdom, also occur in the animal body? This question is of great biological significance, and it also has an important bearing upon human pathology. Seegen, the energetic supporter of the above doctrine, found that, after feeding an animal exclusively on fat, the blood in the hepatic veins contained a considerably larger amount of sugar than the portal vein. We can only put as little faith in this argument as we can in the experiments of Weiss, who found that in the process of digestion of finely-minced liver, to which had been added some neutral fat or some soap, more sugar was formed than if the liver had been digested without either of these two adjuncts. In both cases, even leaving out the question of the technical and analytical difficulties of the experiments, the surplus of sugar may arise from other sources than that of the fat taken as food.

Further, Rohna and Abderhalden have emphatically contradicted the results obtained by Weiss. Therefore there only now remain the experiments on the sugar-eliminating organism which can be accepted with regard to a decision of the above question concerning the transformation of fat into sugar.

To begin with, it must be noted that the question of the formation of sugar from fats is doubtful only in the case of the fatty acids. The transformation of glycerine into glucose, even if it has not yet been explained in detail, is not too difficult a process for chemical comprehension. This transformation has been proved by feeding experiments on phloridzinized animals [Cremer] and upon dogs after removal of the pancreas [Lütze].

Concerning fixed fatty acids, however, matters are quite different, since Rumpf, Hartogh, and Schumm, Rosenquist, and Mohr uphold the statement on the grounds that it has been proved by their own experiments. Von Noorden is a vigorous advocate of this teaching, since he has taken a prominent part in its development.

The results of all these authors prove that an organism affected by diabetes eliminates more sugar than it has taken in in combination with food, and also than it possibly could have formed from transformed protein or from any other sources. This piece of information does not seem to me to be indisputably proved, since in the majority of these observations too low an estimation has been made of the carbohydrate constituents of the food, on the one hand, and the reserve store of glycogen in the body has not sufficiently been taken into account, on the other hand.

For instance, the followers of von Noorden, in their observations, have used as their quotient in working out the amount of sugar derived from albumin the figures $\frac{D}{N} = 2{\cdot}8$, which figures are quite manifestly too low. While it is possible that the quotient $\frac{D}{N} = 4$ (= a formation of 64 grammes sugar from 100 grammes protein), which has frequently been obtained from phloridzinized animals and from men, is too high, it is not permissible to infer that sugar was formed from fat in these experiments.

There is no necessity for further details at this point; for these the reader is referred to the comprehensive review of the above-mentioned experiments which has been compiled by Friedrich Müller and Landergren. Pflüger, the opponent of the doctrine which states that fat is formed from protein, considers this transformation to be certain in the case of fatty acids (11).

That sugar may be formed from fat is evident from the low respiratory quotient during hibernation. The other methods of investigation do not afford convincing proof of this transformation. (See Respiratory Quotient and Muscle Power.)

It must be clearly understood, in spite of the criticism advanced, that we admit the possibility of a formation of sugar from fat in the animal body; but there is an absence of conclusive proofs to support the hypotheses cited. From the results of experiments on diabetes, whether human or experimental, it is evident that the body possesses an urgent need for carbohydrates, and that this need it attempts to meet under all possible circumstances.

When the sugar contained in the food does not suffice for this purpose, the body obtains a further supply from protein, and then only if there is an insufficient supply from this latter source—even if "protein-sugar" is eliminated unused—does the question of the formation of sugar from fats arise.

An increase in the amount of fat-containing food will not—and need not—lead either to an increased formation of sugar, to an accumulation of glycogen, or to the elimination of sugar. The circumstance which governs the transformation of fat into sugar is not *per se* the introduction of fat into the body, but the necessity of the latter for sugar. The relation of fat to the acetone bodies is considered in the following section.

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2. Derivatives of Fat.

The Acetone Bodies.

The connection between the three acetone bodies is a result of their chemical constitution. Acetic acid can be formed in a test-tube from oxybutyric acid by the simple process of oxidation, and from acetic acid acetone may be formed by splitting off carbonic acid gas.

$$CH_3—CH\,.\,OH—CH_2\,.\,COOH + O = CH_3—CO—CH_2—COOH + H_2O,$$
$$\text{and } CH_3—CO—CH_2—COOH = CH_3—CO—CH_3 + CO_2.$$

The same process takes place within the body [Minkowski, Araki, Meyer, Schwarz, and others].

The primary product in the animal body is oxybutyric acid, whose derivation and origin must be explained by those who are endeavouring to ascertain the source and formation of acetone.

Consequences of the Behaviour of the Acetone Bodies.

When the acetone bodies are eliminated in small quantities, then acetone alone is excreted, both in the urine and in the expired air. When the quantity increases, acetic acid also appears in the urine, and if the quantity of acetone bodies eliminated becomes still greater, then also oxybutyric acid is excreted.[1] It must, however, be noted that in a quantitative estimation of acetone not only the preformed acetone,[2] but also the whole amount which has been formed by the decomposition of acetic acid, is included. For a long while we were wrongly content with a quantitative estimation of acetone alone, and altogether neglected oxybutyric acid; but Magnus-Levy has pointed out that in the course of a long-standing and marked elimination of acetone and acetic acid, occurring either in diabetes or even when that disease is absent, besides these two bodies also oxybutyric acid was present in the urine. Sandmeyer (2), has also brought into prominence the fact that these substances occur without exception under the aforementioned conditions in cases of diabetes. Since then more attention has been paid to oxybutyric acid, and whenever accurate observations have been made its presence has almost always been ascertained in the above-named circumstances. Estimations of oxybutyric acid cannot be omitted from further investigations, for frequently it occurs in quantities which are many times larger than those in which acetone occurs, even if diabetes is absent. If decigrammes of acetone are found in a person not suffering from diabetes, frequently the result of an estimation gives quantities of oxybutyric acid from 3 to 7 grammes, or even more, in the selfsame individual [Minkowski, Gerhard, Schlesinger, Magnus-Levy (2)], and in diabetic individuals an extraordinarily larger quantity. An increase in the amount of acetone is therefore a good indication of the increase of the acetone bodies taken on the whole, but of nothing else, since there exists no distinct relation between acetone and oxybutyric acid.

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[1] It appears to be of rare occurrence that, when oxybutyric acid exists in the urine, the two other acetone bodies are absent. Stradelmann (1A), however, reports such a case.

[2] According to the views of many authors, no preformed acetone, but only acetic acid, is to be found in the urine; yet in very slight acetonuria no ferric chloride reaction can be obtained.

For all more comprehensive experiments on this subject, especially with regard to that portion dealing with the derivation of the acetone bodies, other researches are necessary. By such researches are meant not only those dealing with the determination of the acetone in the urine and in the expired air, but also the identification of oxybutyric acid, which is by no means an easy accomplishment when determined analytically.[1] Every theory depending upon this fact must admit that in severe cases of diabetes up to 40 grammes or more of acetone bodies, and in diabetic coma as much as 150 grammes,[2] are eliminated daily.

What can, then, be done if individual authors make far-reaching deductions from an increase or decrease of a few centigrammes in the amount of acetone excreted ?

The Acetone Bodies in Normal Nutrition and in Excessive Carbohydrate Elimination.

Of the three acetone bodies now considered only acetone can be found in the excretions of a well-nourished normal individual. The daily output in the urine is about 1 to 3 centigrammes [von Jaksch, Engel, Hirschfeld, Geelmuyden(3)]; through the lungs a somewhat larger quantity—about 30 to 80 milligrammes [J. Müller]—and none is excreted in the sweat [J. Müller (3)].

Only when the excretion of acetone exceeds this small physiological quantity is it usual to speak of an acetonuria. The conditions for the appearance of acetone have been determined by the fundamental experiments of Rosenfeld and Hirschfeld (4). They determined that, above all, the exclusion of carbohydrates from the metabolism causes acetonuria without exception in the case of man.[3]

After a more or less short duration of acetonuria there also occurs an excretion of acetic acid and oxybutyric acid. A healthy individual excretes considerably increasing amounts of acetone bodies for a number of days when deprived of all food or only of carbohydrates—*i.e.*, when fed exclusively on animal fat (a very instructive series of experiments by Hirschfeld).

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[1] Since acetone and acetic acid are both derived from oxybutyric acid, it is therefore justifiable, in stating the numbers which include the total amount of all three acetone bodies excreted, to convert the amount of acetone and acetic acid into terms of oxybutyric acid.

[2] It must here be emphatically stated that the values for oxybutyric acid which have been ascertained by the lævorotation of fermented urine are absolutely unreliable. The values which have been assigned to it are many times too high.

[3] In animals the conditions are somewhat different.

The following summary shows the observed maximum of a number of metabolism experiments carried out on a healthy individual.

Formerly numerous varieties of acetonuria were distinguished, such as those occurring in inanition, in fever, in infection and intoxication, in diseases of the stomach and intestines, and in nervous and mental affections, etc. All the above-named forms of acetonuria can, however, be referred to the same and identical cause, just as the acetonuria of diabetes can—namely, the entire, or almost entire, deficiency of carbohydrates in the metabolism.

		Acetone in the Urine.	*Acetone in Expired Air.*	*Oxybutyric Acid.*	*Authorities.*
		Grammes.	Grammes.	Grammes.	
Abstention from food.	Two healthy individuals on fourth and fifth fast days	0·5 to 0·78	—	—	Fr. Müller.
	Hysteria; almost entire abstention from food ..	0·3 to 0·4	3·66	+	Nebelthau.
	Melancholia; complete fast	0·6	3·5	+	L. Schwarz.
	Healthy person; second and third fast days	—	—	1·6 to 3·0	Waldvogel.
Meat and fat foods.	Healthy individual; meat and fat eighth day ..	0·5 to 0·87	—	—	Hirschfeld.
	Healthy individual; meat and fat seventh to tenth days	1·3	—	7·0	Gerhardt and Schlesinger.
	Healthy individual; meat and fat second day ..	1·1	++	1·3	L. Mohr.
	Meat with 120 grammes butter first, second, and third days	0·056, 0·144, 0·317	—	—	Geelmuyden.
	Meat with 300 grammes butter first, second, and third days	0·348, 0·953, 0·308	—	—	Geelmuyden.

In children, also, considerable quantities of acetone and oxybutyric acid appear after deprivation of carbohydrate nutriment [L. F. Meyer].

This also applies to the acetonuria occurring during pregnancy and during labour (see section on Influence of Sexual Processes), and also that following extirpation of the cœliac plexus [Lustig], injury of the central nervous system [Oddi], and the administration of narcotics [Becker], even though the discoverers of these occurrences did not make out this connection.

The administration of carbohydrates removes this form of acetonuria within a few days. For this purpose, according to Hirschfeld, 50 to 60 grammes of starch, cane- or grape-sugar are sufficient for an individual who has been fed on animal fat or one who is starving. According to Geelmuyden, larger quantities of sugar—from 100 to 150 grammes—are necessary. Lactose [Meyer] and the other varieties of pure sugars have the same effect, and also mannite [Hirschfeld] and glycerin [Hirschfeld, Meyer], which in the body may be converted into mannitos glucose. Bodies which have less power of reducing acetone, but have a similar effect, are glucose, glycuronic acid (in quantities to 100 grammes) [Schwarz, Mohr and Loeb], and xylose (48 gra on each of two successive days) [Mohr and Loeb]. On the cont the following have no effect: caramel, which is already less cl related to sugar; [Schwarz], lævulinic acid [Weintraud, Meyer], alcohol [Hirschfeld]. An increase of albumin in the food gre diminishes the acetonuria [Hirschfeld, Weintraud, Waldvogel, e probably because when the decomposition of albumin is increase considerably larger amount of carbohydrate is derived from it. Musc work does not influence existing acetonuria [Hirschfeld (7)].

Source of the Acetone Bodies.

The appearance of acetonuria when an individual is deprived of car hydrates at once allows of the exclusion of carbohydrates as being source of derivation of the acetone bodies. That this statement is corr is also proved by the fact that in diabetes acetonuria is very marke and in this disease little or no oxidation of sugar takes place. V. Jaks traces the acetone bodies back to albumin. According to Honigmann a v. Noorden, they are said only to be present when the tissue albumin is split up, and that therefore they are derived from this latter substance. This statement was refuted by Weintraud and Hirschfeld. The first mentioned observed in a case of diabetes an excretion of large quantities of oxybutyric acid for many months, although there was a continuous positive balance of nitrogen (verified by Magnus-Levy and others). However, Hirschfeld, on the other hand, was able to cause the speedy disappearance of all traces of acetonuria in a healthy individual by increasing the amount of carbohydrates in his food, even when, at the time of observation, the body albumin was undergoing disintegration. Consequently, the importance of the splitting up of the tissue albumin for the appearance of acetonuria was refuted, although its derivation from albumin was still adhered to.

This view first began to fall to pieces when the information accrued that under some circumstances more oxybutyric acid is excreted than could be formed from the amount of albumin which is split up simultaneously. Magnus-Levy found in the urine of a patient in a state of diabetic coma 342 grammes of acetone bodies (converted into terms of oxybutyric acid)[1] in three days. From the albumin which could have been disintegrated in this period at the most only 311 grammes of oxybutyric acid could have been derived if the whole of the carbon in the albumin had been converted into oxybutyric acid, which assumption must, of course, be discarded. In view of the importance of these numbers, a reconversion of oxybutyric acid into albumin is impossible, leaving out of the question Sternberg's hypothetical β-amino-butyric acid.

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[1] Here these figures have assigned to them their minimum values on account of the difficulty in determining them. The amount of acetone in the expired air (at least 10 grammes in three days = 18·4 grammes of oxybutyric acid) has not been taken into consideration at all.

Previous to these experiments both Geelmuyden and Rumpf had pointed out the fatty acids—above all, butyric acid—as the probable source of derivation of the acetone bodies. Geelmuyden (1897 and 1898) found that if he added to the food of an individual larger quantities of butter, there was an increase of the existing acetonuria. Therefore he presumed that the low fatty acids of butter, of which butyric acid is present in the largest quantities, were the source from which acetone was derived. Rumpf (1898) noticed in a case of diabetes that oxybutyric acid, which had previously been absent, appeared after giving the patient butyric acid (analytical and quantitative details not being given). Then Magnus-Levy (1899) decided, by the method of exclusion, that, after all, the acetone bodies were derived from fat. This conclusion he arrived at because, since they could not be derived from albumin (according to his figures, already reproduced above), therefore they must be derived from fat. For the formation of the large quantities of acetone bodies which are present in diabetes the preformed quantities of low fatty acids which are present do not suffice. Therefore, according to this author, the higher fatty acids are the chief source of derivation of the acetone bodies—at any rate, in a case of diabetes. The glycerin of fats has nothing to do with the formation of acetone (see above). Further experiments have confirmed this view. When butyric acid, its salts, and butter itself have been given as food, they have nearly always, under suitable circumstances, caused an increase in the quantity of acetone bodies. This has especially been noticed in diabetes, the most favourable condition for any such experiments [Geelmuyden, Schwarz, Loeb,[1] Strauss and Philippsohn]. Butyric acid is a more powerful increaser of acetone than any of the other fats which do not contain low fatty acids. Even these latter fats cause an increase in the quantity of acetone, but to a smaller degree [Waldvegel, Schumann Leclerq, Mohr and Loeb, Grube], and also the higher soaps—*i.e.*, palmitin and stearin soaps [Schwarz].

According to Schwarz, caproic and valerianic acid increase the excretions of oxybutyric acid in diabetes, but propionic acid does not. Whether the increase of oxybutyric acid observed in these experiments is directly derived from the higher fatty acids in the food is not absolutely certain in my estimation, although it must be judged critically on account of the analytical difficulties. It is particularly in diabetes that spontaneous fluctuations are observed.

An increase in the amount of higher fatty acids in the food only increases the fat metabolism in the body to a minimum extent. The fat which is thus taken is either deposited in the tissues or it displaces equal quantities of body fat in the metabolism. But by what means the fat in the food should break up into body fat of the same composition is not very comprehensible. The origin of the acetone bodies of course does not take place in the intestine (see p. 174). In general, considering the therapeutics of nourishment in diabetes, it must be distinctly emphasized that an increase of the fat in food (leaving out of the question the low fatty acids of butter) has no material influence on the formation and elimination of the acetone bodies. This depends, in the first place (according to Pflüger's well-known law regarding the consumption of oxygen), upon the internal condition of the cell. This condition is affected by a deficiency of carbohydrates, and perhaps also by other circumstances, and not at all—or perhaps only to a very slight extent—by the more or less plentiful supply of higher fatty acids.

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[1] 7·0 oxybutyric acid for every 18·7 sodium butyrate.

The transformation of butyric acid into oxybutyric acid is probably brought about by its oxidation in the β-position [Schwarz].

It has not yet been made clear whether butyric acid exhibits the regular course of procedure in the formation of oxy-acids from the high fatty acids. In any case, then, there must be formed from each molecule of higher fatty acids more than one molecule of butyric and oxybutyric acid, the carbohydrate chain being broken up. Otherwise quite impossible figures would be obtained representing the total fat exchange [Magnus-Levy]. A still further possibility for the derivation of oxybutyric acid has been suggested by Spiro and Magnus-Levy.

Just as butyric acid is synthetically formed by the process of fermentation from two chains, each of which has two carbon atoms—

$$2CH_3\text{—}CHO = CH_3\text{—}CH_2\text{—}CH_2\text{—}COOH.$$

—so could butyric acid also be formed from them, if in this process an oxidation were simultaneously taking place (oxidative synthesis).

$$2CH_3\text{—}CHO + O = CH_3\text{—}CHOH\text{—}CH_2\text{—}COOH.$$

Up to the present time there has been no definite proof of this hypothesis.

It is quite certain that the fats yield the chief material necessary for the formation of the acetone bodies. Yet the possibility of small quantities of acetone bodies being derived from albumin and carbohydrates must be discussed, not only because of the fact that acetone is formed when carbohydrates, gelatin [Blumenthal and Neuberg], and albumin [Orgler] are artificially oxidized, but also because oxybutyric acid, the chief of the three acetone bodies, has not been observed in these experiments. But this possibility must, on these theoretical grounds, be allowed; for butyric acid, which is one of the stages in the formation of oxybutyric acid, can be formed from albumin and carbohydrate. This takes place not only in bacterial processes, but also very probably in the tissues of the higher animals. Moreover, the hypothesis of a synthetical formation of oxybutyric acid suggests a possibility that it may also be derived from other bodies besides fat, for substances having in their composition two carbon atoms can, without doubt, also be formed in the breaking up of albumin (and of carbohydrates). Any questions concerning the origin of certain metabolic products of the various foodstuffs must nowadays be summed up much more strictly and in quite a different manner than formerly. For to-day it is known that a partial conversion of the three great groups of food-stuffs one into the other can take place. From albumin, both sugar and (by removing the amido group) oxy-fatty acids, probably low fatty acids, and, it is stated also, fat, can be formed. From sugar fat is formed, and perhaps the opposite process takes place in the animal body. A body, therefore, which is directly derived from carbohydrates—as, for instance, glycuronic acid—can also be formed from " albumin-sugar." Lactic acid, which is produced in the breaking-up of grape-sugar, is, under some circumstances, formed in the animal body from alanin [Langstein and Neuberg]. Low fatty monobasic acids and oxalic acid can be formed by oxidation from all the three classes of food-stuffs. In considering, therefore, the question of the derivation of such metabolic products, the following points have to be elucidated : Firstly, their special mode of derivation ; secondly, the various steps in the process ; and finally, the events which immediately precede their derivation.

On the other hand, if there is any question about a substance being derived from several sources, it must be decided which of them comes into prominence quantitatively. So, according to our opinion, the amount of lactose formed from alanin (albumin) is far behind that formed from grape-sugar. In the case of the acetone bodies, we thus come to the conclusion that both they themselves and their immediate antecedents (butyric acid or carbohydrate chain with two carbon atoms) can be formed from fat, albumin, and carbohydrates ; but that in the body they are actually formed in by far the largest quantities from the fats, their formation from albumin and carbohydrates being, if of any, only of small account.

Sites of Formation of the Acetone Bodies.

Formerly the alimentary canal was frequently regarded as the site of formation of the acetone bodies, probably partly on account of analogical conclusions (the formation of putrefactive and other fermentative products in the intestine), and partly because of the presence of iodoform-forming bodies in the excreta and in vomited material. This is certainly incorrect. When the intestines are disinfected with calomel [Lüthje], existing acetonuria remains uninfluenced. An observation of the large quantity which is excreted in cases of diabetes is here quite conclusive and decisive. Quantities of 40 to 100 grammes of oxybutyric acid can surely not be formed in the intestines, and must be formed in the body itself [Magnus-Levy]. Besides the muscles and the liver, which are naturally placed first when such a large formation takes place, other organs of the body, and perhaps all of them, have to be taken into consideration. Even healthy organs almost constantly contain small quantities of acetone or iodoform-yielding bodies [v. Jaksch, Geelmuyden]. Much larger quantities of acetone—from 70 to 100 grammes—can be obtained from the organs of a diabetic [Magnus-Levy, Geelmuyden]. In this illness the tissues also contain larger amounts of oxybutyric acid —up to 0·2 per cent., or even more [Hugounneng, Magnus-Levy]. Also, if oxybutyric acid is excreted when diabetes is not present, it may be found in the body [Schwarz in a case of melancholia]. When a substance is as easily diffusible as are the acetone bodies, the amount present in a single organ gives no clue to the principal site of formation of the substance (*cf.* urea and liver). The acetone which is found in the contents of the alimentary canal [von Jaksch and others] has most probably been excreted into this situation by the body. Magnus-Levy also takes a (post-mortem ?) diffusion for granted in the case in which he found oxybutyric acid in the stomach contents of a patient who had died in a state of diabetic coma.

The Acetone Bodies as Intermediate Products of Metabolism.

Are the acetone bodies normal products of intermediary metabolism ? It is certainly the case that the urine and expired air of healthy men contain traces of acetone.

The question is whether quantities of 40 to 150 grammes, which occur in the worst cases of diabetes, also appear in the healthy organism regularly as an intermediate product. If this were the case, then their elimination, when there is a deficiency of carbohydrates, would arise from lowered oxidation powers of the tissues. The authors who consider this as being probable take for granted a " secondary oxidation " of acetone bodies by means of a simultaneous combustion of carbohydrates [Naunyn]. Geelmuyden considers that there is a direct union of the acetone bodies with the carbohydrate derivatives. (A combination of the acetone bodies with glycuronic acid cannot easily be imagined.) However, it is quite certain that in those circumstances under which there is a large excretion of acetone bodies the power of combustion for these substances, when they are used as food, is reduced. For, while the healthy organism consumes[1] acetone bodies almost completely when they are introduced into the body, under any other conditions oxybutyric acid and acetic acid are partly excreted as such, and partly as acetone. These " other conditions " just referred to are : poisoning with carbonic oxide gas [Araki], extirpation of the pancreas [Minkowski, Schwarz], poisoning of an animal with phloridzin or exclusive feeding of a person on animal fats [Geelmuyden], and lastly, severe cases of diabetes.

The oxidizing power for these substances (acetone bodies) is also probably lost in cases of severe diabetes [Magnus-Levy (15)]. This diminution of oxidizing power in the above-mentioned abnormal conditions might be regarded as a possibility of the regular appearance of acetone bodies as an intermediate step in the normal metabolism.

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[1] The sodium salt of inactive oxybutyric acid was given as food by Weintraud, Meyer, Araki, Magnus-Levy, Zeehuysen, MacKenzie ; the sodium salt of the lævorotatory acid was given by Minkowski, Waldvogel, Schwarz, and the dextrorotatory acid by Sternberg. Essentially these three modifications behave in the same manner, but the dextrorotatory appears to be more easily decomposed than the lævorotatory acid [MacKenzie]. Quantities up to 25 grammes are entirely oxidized by a normal individual. Dogs only excrete oxybutyric acid after the introduction of more than 2 grammes per kilogramme. Acetic acid and acetone appear in the urine as products of decomposition, especially when oxidation is disturbed. Geelmuyden has lately performed some excellent quantitative feeding experiments with acetic acid both in the human being and in the dog. Acetone which has been introduced into the body in this manner is excreted in considerable quantities unchanged [Schwarz, Geelmuyden].

However, it seems more probable that they are not regular intermediate metabolic products, but that their formation in any remarkable quantity is, in the first place, caused by lack of carbohydrates. It is only when the organism of the omnivorous human being (the dog and rabbit behaving differently in this respect) is condemned to a diet which, besides albumin, consists solely of fats, that in their utilization there are derived from them acetone bodies. The grounds for this process and its purpose are yet unknown.

Influence of Alkalis and Acids upon the Excretion of Acetone Bodies.

In the normal organism they appear to have no influence on this process. In cases where there is occurring a large excretion of acetone bodies, as in diabetes, the excretion can be considerably increased in amount by giving large quantities of alkalis [Weintraud]. According to Magnus-Levy, whose statement of figures is particularly instructive, this does not necessarily depend upon a disturbance of oxidation, which has been caused by the sodium given. His explanation is that the acid is more quickly eliminated in a form in which it can easily be taken up by the urine, which removes a portion of the acid, which is otherwise burned up. Meyer, Gerhardt and Schlesinger, Mohr and Loeb, also found an increase of acetone when giving large quantities of sodium bicarbonate. In other cases no increase was noticed [Weintraud, Mohr, and Loeb]. Certainly various influences are at work both in the formation and the excretion of the acetone bodies. Hydrochloric acid, according to Weintraud, increases the excretion of acetone in diabetes (16). Concerning the relation of the excretion of oxybutyric acid to the increase of ammonia in the urine, see the section on Ammonia. The appearance of large quantities of non-combustible organic acids in the metabolism was designated by Naunyn as "acidosis."[1]

With regard to the quantity of acid products which are abnormally excreted, by far the most prominent position in human pathology is occupied by the acidosis of oxybutyric acid. Next in importance comes the excretion of lactic acid, for in liver diseases in the human being quantities varying from 10 to 20 grammes may occur in the urine.

Other forms of acidosis, such as lipaciduria, an abnormal increase of oxalic acid, of uric acid, and of aromatic acids, occur in much smaller quantities. It must be here remarked that the acidosis of oxybutyric acid has no connection whatever with that of lactic acid. Both of them are proofs of some disturbance in the metabolism, but they can exist independently, even if they occasionally appear at the same time. Oxybutyric acid is always found in the urine without lactic acid being present at the same time, and, *vice versa*, lactic acid is found without oxybutyric acid. Lüthje (17) therefore missed acetone in the urine during epileptic convulsions, when lactic acid is very frequently present.

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[1] The relative "acidosis" of Steinitz is quite a different matter, although it has, in common with the true acidosis of Naunyn, an increase of ammonia in the urine. It is not an absolute increase of acids, but a relative predomination of them, which is a normal occurrence in consequence of the deprivation of carbohydrates. This is described fully in the chapter on ammonia.

(In this condition acetone bodies could quite possibly appear, just as they do in cases of strychnine-poisoning, when carbohydrates disappear in large quantities, and without speedy compensation, during convulsions of long duration.)

Acidosis, particularly that brought about by oxybutyric acid, frequently appears when a diseased or healthy individual is getting only half the amount of his usual quantity of food, and does not, as a rule, cause immediate or gradually developing disturbances to occur, the regulating mechanism in the human body being too perfect. It is only when greater quantities are present, and after some duration, that disturbances or damage to the stock of alkalis, etc., occurs. The quantity in which the acids may be present without causing symptoms has not yet been minutely determined, but it must not be overestimated. A diabetic can feel quite well for years, even if he is suffering from an acidosis of 10 to 20 grammes, or even more, of oxybutyric acid. It would not be correct in an illness, if a few grammes of an acid be present, which in itself is non-poisonous, to ascribe the cause of the harm of the disease to this " acidosis." " Acidosis " and " fatal poisoning by acids " [Magnus-Levy (18)] do not differ from one another very much in their causation, but they do so in their course.

The first-mentioned event happens very frequently, but the latter has only been proved up to the present to occur in cases of diabetic coma. Concerning the relationship of acidosis to ammonia, see section on Ammonia.

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3. The Alkalinity of the Blood.

Blood is a neutral liquid when regarded from the point of view of the ion theory [Maly, Friedenthal, Höber, Fraenkel, Farkas (1)], but this physico-chemical view is at the present time not a matter of great importance for the physiologist and the physician. In all practical discussions on the question, the blood must be regarded as an alkaline medium. Its power of transporting carbonic acid depends upon the alkalinity of the blood, and upon this fact is also dependent the power of the blood to take up, at certain times, organic acids without itself becoming acid. For a long while too much attention has been paid to the alteration in its alkalinity, but the interpretation of the result of these researches has not everywhere obtained full agreement and conformity. This is due partly to the large number and the various significances of the methods employed. Therefore a few critical remarks ought to be made concerning them.

Three types of bodies must be taken into consideration in studying the reaction of the blood :

1. The behaviour of its mineral constituents. The value of the alkaline exceeds that of the acid ones, the quantitative interpretation of their predominance being the " mineral alkalinity of the blood."

2. The occurrence of volatile, and for the most part organic, bases and acids in the blood, and also of ammonia, lactic acid, uric acid, etc. The quantity of these bodies present in normal blood is so minute that their significance as regarding the extent of the alkalinity, as opposed to that of the carbon constituents, quite falls into the background.

However, under pathological conditions, their increase, especially that of organic acids (lactic acid in those suffering from liver disease, oxybutyric acid in cases of diabetes), etc., can be of so much importance as to seriously influence the total alkalinity of the blood.

3. The existence of bodies which, without being alkaline or acid in the chemical sense, can combine with alkalis or acids, such as albumins.

For a determination of the alkalinity of the blood, the four following methods, which differ in principle, may be adopted :

1. Determination of the alkalinity of the blood by an analysis of its mineral constituents, provided that their valences are not firmly bound up organically, as, for instance, is the case with the sulphur of albumin, and the organic phosphorus. Kraus (2) has calculated the following values for the mineral alkalinity of horse's blood from Abderhalden's analysis :

100 c.c. of serum = 187 milligrammes of NaOH.
100 c.c. of blood = 230 milligrammes of NaOH.

Since the alkalinity of the blood depends in the first place upon its mineral alkaline constituents, a full knowledge of their properties is a matter of great importance. But on account of the great labour this entails, and the large amount of material necessary, the above estimation would scarcely be applicable in the case of human blood. On the other hand, in the exclusive determination of the alkalinity of the blood, the presence of organic acids would be quite overlooked. For, if it is considered that in cases of diabetic coma up to 200 milligrammes of oxybutyric acid may be found in the blood, and that this amount can neutralize about 80 milligrammes of NaOH, then the omission of the organic acids would lead to an utter misconception of the real facts.

2. The direct titration of the blood, using indicators. The older method of titrating blood of the colour in which it occurs in the body has been discarded, although this method disclosed many important facts in comparative experiments. This method has fallen into disuse ever since Loewy (3) showed that some alkaline constituents remain enclosed in the undisturbed blood-corpuscles, and thus are withheld from

titration. Instead of this process, during the last ten years there has come into use the oft-tried method of Loewy—that of laked blood. The figures obtained by this method, as representing the alkalinity of the blood, are far higher than those obtained by any other method. Loewy gives the following values: for horse-blood, 100 c.c. = 344 to 544 milligrammes, and for normal human blood, 447 to 508 milligrammes of NaOH. In this estimation the valences of albumin and other neutral bodies for acids have been included (subalkaline bodies). That the albumin of the blood as subacid material is able to bind up varying amounts of alkalis under ordinary circumstances, and really does so, is discussed under heading No. 4. What part is played biologically by the valence of albumin (regarded both as a subalkaline and as an acid-binding body) which has been discovered by Loewy's experiments is, for the main part, unknown. It may be thought that it binds up a portion of the organic acids when these latter bodies appear in the blood, and therefore partially protects the fixed alkalinity of the blood at intervals. This action is intermittent, since, when these acids appear in the urine, a dissociation must take place, and the acids must become linked to ammonia or to a fixed alkali. But above everything else (and this is an important consideration), the extent of the acid capacity of the blood-proteins is artificial, as far as we are able to determine it at the time, and it also depends upon the manner of titration [see Spiro-Pemsel (4)].

Again, the most careful carrying out of Loewy's instructions leads to values which in the hands of different observers are quite dissimilar from his own. Such divergent and self-contradictory results have been obtained, especially in pathological conditions, that the intrinsic value and significance of this method are not yet settled. The simultaneous determination of the protein-nitrogen may be considered a necessary supplement to the method, and is extensively practised; but the differences observed are in no way explained by the disproportionate amount of the blood-albumin.

3. The titration of the blood after precipitation of the total protein by ammonium sulphate, which is the general principle underlying the methods of F. Kraus, Spiro-Pemsel, Salkowski, and Salaskin (5), completely disposes of the acid-combining valences of protein. If during precipitation no acid or basic constituents, or at all events not more basic than acid valences, be thrown down—a fact which Kraus[1] (1) maintains, though Spiro-Pemsel does not quite agree to—so one by this kind of procedure would obtain the mineral alkalinity increased or reduced according to the actual basic and acid valences of organic substances. This method requires further use and more extended application than it has yet found. Kraus, from his methods, gives the alkalinity value for 100 c.c. of normal human blood-serum as 120 to 126 milligrammes of NaOH, that of the blood as 188 to 220 milligrammes of NaOH.

4. The determination of the amount of CO_2 in venous (certainly less applicable to arterial) blood was first employed by Walther as a measure of the alkalinity of the blood. It is preferred to all other methods

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[1] Kraus finds by his method in normal blood of animals the same values as for the mineral alkalinity. Spiro and Pemsel's figures are 25 to 30 per cent. less.

by Hans Meyer (6), also a pupil of Schmiedeberg's. It demonstrates only a portion of the mineral alkalinity—in fact, that portion whose significance must be considered. Under normal conditions, one rarely finds more or less than 50 c.c. of carbonic acid (= 98 milligrammes of CO_2) in venous blood. These 98 milligrammes (132 milligrammes if it is present exclusively as bicarbonate)[1] can, if they be present half as monocarbonate and half as bicarbonate, combine with 176 milligrammes of NaOH. As the mineral alkalinity is higher—at least, in certain animals—then the excess must combine with protein, because "free soda" is not present in the blood. That this really is the case follows from the diffusion experiments of Guerber, Zuntz, and Loewy (7) (non-diffusible alkali). In the capillaries of the lungs, a part of the alkali, after evaporation of the carbonic acid, must pass over to the protein, and *vice versa* in the capillaries of the organs. The blood alkalinity, as determined by means of the CO_2 constituent, is thus quite different in arterial and venous blood, although the alkali constituents in both are similar, or almost so. This method, in fact, has permitted a demonstration of the lowering of the carbonic acid constituent in accordance with the results obtained by other methods, where an acidifying of the blood is effected (or apparently so) by organic acids, as in the case of experimental acid-poisoning [Walther (6)], in diabetic coma [Minkowski, F. Kraus (8)], in fever [Minkowski (9)], and in toxæmia [Hans Meyer (6)]. Nevertheless, the carbonic acid constituent of venous blood may be regarded neither as the absolutely correct measure of the blood alkalinity, nor as the only applicable comparative procedure. For the carbonic acid constituent of the blood depends—besides the absorptive capacity of the blood and its alkalinity—above all, upon the rapidity of the absorption and removal—that is to say, upon the extent of the carbonic acid formation in the tissues, and upon the rapidity of evaporation from the lungs. The extraordinary diminution of carbonic acid in the blood of rabbits[2] poisoned with acids, as found by Walther, depends partly on the powerful lung ventilation in addition to a partial neutralization of the alkali. This is also a concomitant sequel of the administration of acids [Kurt Lehmann (10)]. In fact, Loewy and Münzer have shown that the venous blood, which in a rabbit poisoned with acids contains only 6 to 17 per cent. of CO_2, can still chemically combine with 13 to 18 per cent. of CO_2 on shaking it up with an atmosphere containing 5 to 7 per cent. of CO_2. There was thus by no means so much NaOH combined with the administered acid as had previously been accepted, owing to the low CO_2 percentage. Chvostek has also shown that the formation of CO_2 is diminished in poisoning by acids, as was previously conjectured.

Value of Comparative Estimations with the same Method.

The explanations stated in the previous paragraph essentially discuss the fundamental differences in the significance of the "blood-alkalinity" values obtained by the different methods. Which of them should be considered as the "theoretically correct" one, and employed as being practically the more important, cannot be definitely decided. In future, several "alkalinity-values" must be taken for an explanation of the different points of view, and their significance determined by comparative examination. Still, the question arises as to the value of different estimations by means of one and the same method. There is a tendency, in many cases, to apportion to such comparative researches a great significance and far-reaching value, even if the methods be uncertain in themselves. This is only permissible to a certain extent, and it is quite as little suitable as the too often accepted conclusion that an analysis is accurate, for the reason that a control analysis with the same method furnishes the same results. Certainly, marked to-and-fro fluctuations are recognisable in comparative researches in which one and the same method is employed, this being an outcome of the apparent variation of alkalinity by employment of different methods. Still, the absolute variation of the former is to be judged very critically. This has been already pointed out in the case of the CO_2 estimations. These considerations apply in still higher degree to Loewy's method, in which not only the extent of the variation, but also its direction (diminution instead of increase, and *vice versa*), awakens, here and there, a doubt as to the utility of the procedure.

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[1] According to Friedenthal and P. Fraenkel (1), bicarbonate is alone present in blood and serum.

[2] And perhaps also that in diabetic coma.

Yet another consideration in regard to alkalinity estimations must be here referred to, and this is equally applicable to all methods. As a rule, venous blood is taken for the estimations, although its alkalinity in the different vascular areas, and even in the same area with varying activity of the organs, varies at different times. If at one time acid substances become formed in larger quantity in muscle or abdominal organs, and are carried by the nearest circulation into other organs for combustion, then the diminution of alkalinity of the total venous blood, by employing blood from cutaneous veins, would not in such a case correctly express the condition. In addition, the varying velocity of the blood-stream, the production of a greater or less stasis during the collection of the blood, also influences the results. This applies particularly to the method of estimating the carbonic acid contents. Theoretically, therefore, the alkalinity should be determined in mixed venous or in arterial blood, but in man this is, of course, impossible. (A full account of the methods of blood alkalinity is given by Gamble (12). He uses alcoholic lacmoid solution as the indicator, and states that the average alkalinity of the blood of normal healthy adults is 300 milligrammes NaOH for 100 c.c.)

The blood-serum and the lymph are less alkaline than the blood. That of the tissues also appears to be less. Yet for its estimation there is as yet no other method at our disposal than the decidedly questionable one of analyzing the ash.

Administered alkali leaves the body fairly soon after absorption, so that, after large doses of alkali, only a part of it is really present in the organism at any given time. Accurate determination by two or three hourly experiments are wanted. How this alkali is retained in the blood, how much of it at any stated time is present in the blood and lymph, what quantities pass into the different tissues and organs, is not exactly known. And yet an accurate knowledge of this point would be of great significance for science and for practice. The possibility of variations of alkalinity in the tissues, though often challenged by therapeutists, must be admitted, although their amount and duration are not yet determined.

In some chapters of this physiological section certain statements regarding the blood alkalinity are made. The above discussions may teach how carefully they are to be judged. This remark applies, not only to physiological conditions, but even more to pathological changes.

Few other domains of physiology are in such urgent need of further enlightenment as that of the alkalinity of the blood. The theory of ions, which we have intentionally left out of consideration, must be introduced to a certain extent into the realm of the discussions. But the subject needs, above all, critical experimental comparison of the different methods. Upon a thorough work of this type depends the possibility of favourably applying the alkalinity of the blood to theory and practice (12, 13).

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D.—FATE OF ALCOHOL.

Exchange and excretion of alcohol are described in another section in connection with other considerations. See section by O. Loewy.

IV

METABOLISM IN MAN

A.—THE TOTAL ENERGY EXCHANGE.

1. Extent and Measurement of the Exchange of Energy.

The Exchange of Material.—The total exchange of material may be measured by the amount of energy furnished by the metabolized materials in terms of heat units or calories. Rubner (1) first initiated this principle, and his are the standard numbers in use at the present day. He showed by means of new methods, with due regard to the essentials, that within certain limits the food-stuffs each represent a relation to the amount of heat arising in the organism from them. He fixed the "physiological combustion values," and, by his brilliant calorimetric researches on animals, furnished the information that the law of the conservation of energy holds good also for the animal body. The amount of heat given off from the animals in his experiments was actually, within the error limit, the same as that calculated from the exchange (1).

All energy set free in the body leaves the body as heat, in so far as energy of work is not transferred outwards, and this is generally not the case in such experiments. The figures supplied by Rubner for the physiological combustion values of food-stuffs, and for their representation in relation to one another, still hold good to-day for practical purposes. For some purely scientific considerations—for example, that of the food and heat values of protein and meat, and many other particulars—the work of standardization still goes on, just as in physics and astronomy certain cardinal numbers must be again and again determined anew with the progress of technical methods and the knowledge of new influences. For practical experiments the following mean values are employed [Rubner (2)]:

Energy contained in 1 gramme of protein = 4·1 calories.
" " " " starch = 4·1 "
" " " " fat = 9·3 "
" " " " alcohol = 7·0 "

From the amount of the "absorbed food-stuff" (food minus excrement) one calculates with these numbers the tonicity supplied to the body. In the case of alcohol, one requires to deduct a certain percentage for excretion by the urine and respired air.

Some sources of error are present here, although for most experiments in which the highest scientific accuracy are unnecessary they do not really carry much weight. In the first place, for the calculation of protein. In Rubner's mean value of 4·1 calories for 1 gramme of albumin the removal of the nitrogenous substance contained in the excreta is already considered, and yet the nitrogen of the excreta in most balance-sheets is placed in the reckoning a second time as unabsorbed protein substance. Further, the percentage of the carbohydrate in the excreta is only rarely determined directly; the loss from defective absorption is, on the other hand, quite neglected or found too high, if the carbohydrate percentage in the excreta is ascertained indirectly (dried substance minus protein, fat, and salts). The following procedure, which is already much employed in physiological laboratories, permits of the available supply of energy being estimated free from error. The total food (*a*) is calorimetrically analyzed in the composition or preparation in which it is actually assimilated; in a similar way the urine (*b*) and the fæces (*c*); $(a-(b+c))$ is then the available heat supplied to the body. Still, excretions in the perspiration and in the expired air, such as alcohol, acetone, etc., need consideration at times.

Practical Estimations of the Exchange of Energy.

Direct and Indirect Calorimetry.[1]

By the application of this uniform standard it is alone possible to compare the exchange of material in different individuals and in different animal classes. The estimation which is most appropriate up to a certain extent—the direct calorimetric investigation—has, thanks to the splendid technical methods of Atwater (3), been accomplished for man with brilliant results. But practice and also science are, as a rule, obliged to develop without it. They can do this in virtue of the fact that the knowledge of consumed food-stuffs permits one to reckon the heat exchange directly. The indirect methods which are in use to-day for measuring the exchange of energy are founded entirely on the estimation of the transformed food-stuffs. These, on their side, can be fairly well estimated by a consideration of the administered food and drink (and in certain cases also the absorbed oxygen) from the excreted nitrogen and carbon (CO_2).

Two or three methods of research are at our disposal. These have been long regarded as contradictory. According to the worker's standpoint, the value of the one or the other system has been constantly and wrongly underestimated. These methods are not fundamentally distinct from one another, and are not unequal in value; the absence of the one or the other would constitute a serious loss for theory and practice. Regarding this, it must be made clear as to what purposes one will and can attain with both, what advantages or disadvantages they show, and where the limits of their application lie.

The one experimental procedure depends on the measure of the excreted carbonic acid for prolonged periods—of twenty-four hours at the most. It takes its origin from Pettenkofer and Voit, and has further experienced manifold technical improvements and striking scientific perfection at the hands of Rubner. It lies also at the foundation of the researches and apparatus of the great agricultural institutes, as those of Sweden [Tigerstedt] and the American observers [Atwater]. The other method estimates the gas exchange in the lung—that is, the absorption of oxygen and the exhalation of carbonic acid—in experiments of brief duration (lasting from about ten minutes to an hour). It is the older method, used later by English and French observers (indeed, mostly with a neglect of the oxygen estimation [Andral and Gavarret, Smith, and others]), and further elaborated by Speck. It has reached its present stage through Zuntz, and has been made applicable, within the most extensive limits, for physiology and pathology. The techniques will be hereafter entitled — the briefly prolonged estimation of lung respiration, as the Zuntz method, and the long delayed, as the Pettenkofer-Voit principle.

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[1] *Cf.* also a new form of respiration calorimeter with appliances for the direct determination of oxygen. Atwater and Benedict, Washington, Carnegie Institution, 1905.

There is a third experimental method, in which, just as in the Pettenkofer procedure, the carbonic acid is estimated, and likewise the oxygen for prolonged periods [Reignault-Reiset, F. Hoppe-Seyler, Jaquet], attempts being made to blend the advantages of both methods. We need refer to it only briefly, as it hitherto has been only little applied. Extended trial of the Jaquet apparatus, and especially as soon as America will have presented us through Atwater with trustworthy apparatus, may furnish decisive results.

Method of Pettenkofer and Voit.

In the Pettenkofer-Voit method the total amount of carbonic acid expired from the lungs and skin (besides the excreted water) is estimated generally in experiments of twenty-four hours' duration. To the carbon given off by the respiration is added that of the urine (and by individual authors also a part of the carbon in the fæces), and thus the total quantity of consumed carbon determined. The origin of this carbon from the various food-stuffs is estimated as follows : In the first place, the quantity of carbon corresponding to the consumed protein is deducted from the total sum.[1] The remainder is divided into alcohol, carbohydrate, and fats, other substances not coming into consideration on account of their minute quantities. It is here assumed that alcohol is practically completely consumed to minute traces. This is correct, as it never becomes stored up in the body, and carbohydrate becomes oxidized before the fats. The total administered alcohol,[2] with its carbon constituent, is next added, together with the absorbed carbohydrate. Any carbon residue then remaining will be considered as originating from the combustion of fat, and from it the amount of fat oxidized is calculated. In fasting experiments, next to protein, fat only will be considered as entering into combustion.[1] From the consumed food-stuffs thus estimated the amount of heat or energy set free is readily calculated from Rubner's figures. The following table, taken from a work of Clopatt (4), gives an example of such a calculation :

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[1] Metabolized protein = 6·25 of urinary nitrogen = 3·28 grammes of protein carbon. Individual authors add to this 1 gramme as the nitrogen of the fæces = 3·28 grammes carbon as originating from the digestive juices, and corresponding, therefore, to decomposed protein.

[2] After deducting 2 to 10 per cent. which is excreted unconsumed. See the section on Alcohol.

EXCRETED.		*N* Grammes.	*C* Grammes.
In the expired air (758·8 grammes CO_2)	=	—	206·92
In the urine	=	11·85	10·67[2]
In the fæces (from digestive juices)	=	1·00[2]	3·28[2]
Total	=	12·85	220.87

DECOMPOSED.		*C* Grammes.	*Cal.*
Protein (=12·85 N × 6·25=) 80·31 grammes	=	42·15	329·3
Alcohol=(90 per cent.[2]) consumed 87·0=78·34 grammes	=	40·87	548·4
Carbohydrates (all absorbed)=244·95 grammes ..	=	106·80	1004·3
Fat (remainder of CO_2, 31·05)=40·59 grammes ..	=	31·05	377·5
Total	=	220·87	2259·5

Criticism of the Pettenkofer-Voit Method.

The advantage of this method lies in the fact that the metabolized food-stuffs (and especially the amount of protein from the twenty-four hourly nitrogen excretion) permit of being fairly well calculated. Moreover, periodic variations of the CO_2 excretion occasioned by irregular respiration are completely balanced by the long duration of the experiment. A further advantage consists in the possibility to measure the amount of water given off from the lungs and skin. This is less important for the estimation of the energy exchange than for the determination of a water balance, etc. The box or chamber shaped apparatus of Pettenkofer and his followers permits of an excellent study of the action of differences in the surrounding temperature and humidity of the air. More than that, an essential advantage lies in the fact that the researches with apparatus of this sort take place under proportionately natural external conditions, which are fairly similar to the actual conditions of life in man.

Thus, this method permits one to settle the actual daily metabolism with wellnigh complete certainty and trustworthiness. In reference to food-stuff requirements and rational nourishment, to the setting up of a sufficient daily balance, to the estimation of diet cures, or hunger and partial fasting experiments, it is a standard, and therefore decisive. The questions of practical nourishment are essentially influenced and decided by it. Moreover, it suffices for the claims of hygiene, which, after all, is but physiology applied to the conditions of practical life.

But this method has also its drawbacks. There are fixed limits to its intrinsic value. Its disadvantages consist firstly in the fact that it is applicable only for prolonged periods.[1] This restriction excludes its application for the study of all those influences which act for short periods only. The transient course of tissue changes does not allow of good results from its use. A second fault is the remarkable and inevitable omission of a direct estimation of the consumed oxygen. If this be essentially superfluous for several days' balance experiments, then its absence still signifies a termination of the investigation of the transient course and of the extent of the carbohydrate combustion, and so on. The chief disadvantage, however, lies in the fact that we learn to know fairly precisely the total of all actions influencing the tissue change over long periods, so that, on the other hand, we cannot differentiate the significance and action of the individual factors from each other, or, at least, not so sharply as with the method now to be described.

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[1] For a source of error here, see p. 192.

[2] These values are those found in earlier experiments, and not estimated for this one.

Method of Zuntz.

In the Zuntz method only the exchange of gas in the lung is measured during brief periods. Here the estimation of the carbonic acid discharged from the skin and that of the excreted water is omitted. Therefore, in addition to the carbonic acid excretion, the much more important oxygen absorption is determined, and the respiratory mechanism simultaneously taken into consideration.

The calculation rests in the main on principles similar to those of the Pettenkofer method—namely, on the estimation of the metabolized foodstuffs, and the heat arising therefrom. The amount of protein metabolized, just as in that case, is determined from the nitrogen of the urine. An exact calculation as to how much fat and how much carbohydrate are consumed in addition to the protein is not necessary, as the heat production can be directly calculated from the consumed oxygen without having determined the oxidized combustible material beforehand. This method is based upon the following consideration : By the oxidation to its end-products at any time of a material of known composition, a definite amount of oxygen will be consumed for every gramme of consumed material, a definite amount of carbonic acid formed, and a definite amount of heat developed. The weight or volume unit of consumed oxygen (or carbonic acid formed) thus corresponds to a definite amount of liberated heat, which we denote as the caloric factor of oxygen (or carbonic acid), (Cal. (O_2) and Cal. (CO_2)).

One gramme of starch yields the following figures :

1 gramme of starch uses 828·8 c.c. O_2.[2]
1 gramme of starch forms 828·8 c.c. CO_2.
1 gramme of starch develops 4·1825 cal.

The resp. quot. amounts to 1·00.
5·047 calories correspond to 1 c.c. O_2.
5·047 calories correspond to 1 c.c. CO_2.

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[1] Rubner's own experiments nearly always lasted more than four hours. The Swedish observers (Johannson and others) have, indeed, succeeded in applying the method also for brief periods—as low as half an hour. These short experiments, however, approximate in principle to the procedure of Zuntz. They renounce all claim to the advantages of the setting up of an exact balance, without exchanging for that the advantages of the estimation of oxygen.

[2] All estimations of CO_2 and O_2 in this book are calculated for the latitude of Berlin. In Berlin 1 litre of O_2=1·430, and 1 litre of CO_2=1·966 grammes.

The calculation of the amount of heat formed from the consumed oxygen would not be subject to further considerations if only one food-stuff was actually and completely consumed. On the other hand, if different food-stuffs become oxidized, the caloric factor of oxygen varies for the different substances concerned. The following table provides an explanation of this. It shows, in the first place, that the caloric values of oxygen deviate less from one another than those of carbonic acid; that is thus the chief cause of the exchange of energy in all experiments by the Zuntz procedure being calculated from the consumption of oxygen, besides the circumstance that the absorption of oxygen is far less acted upon by external influences than the expiration of carbonic acid. The estimation of carbonic acid has more secondary value in that it yields the respiratory quotients, and in this way denotes the kind of the consumed food-stuffs.

The calculation is effected as follows: In the first place, the gas exchange is calculated on the time unit (on a minute or an hour). The protein metabolism occurring in this period is calculated from the nitrogen of the urine (either from that passed during the experimental period or during twenty-four hours). The amount of oxygen and carbonic acid corresponding to the oxidized protein is deducted from the total oxygen and the total carbonic acid. The respiratory quotient is calculated for what remains of the O_2 and the CO_2. This remainder arises from the combustion of fat and carbohydrate when alcohol has not been taken during the preceding hours. How great the proportion of both these is, and what caloric value belongs to the consumed oxygen, may be ascertained directly from the height of the respiratory quotient of that remainder, according to the following point of view originated by Zuntz (5):

1 Gramme.	*Required for Oxidation (c.c. O_2).*	*Formed during Oxidation (c.c. CO_2).*	*R.Q.*	*Developed Cal.*	$\frac{c.c.\ O_2}{Cal.}$ = *Cal.* O_2 *1 c.c.* O_2 *yields Cal.*	$\frac{c.c.\ CO_2}{Cal.}$ = *Cal.* CO_2 *1 c.c.* CO_2 *yields Cal.*
Starch[a] -	828·8	828·8	1·000	4·1825	5·047	(5·047)
Animal fat[a]	2019·2	1427·3	0·707	9·461[a]	4·686[b]	(6·629)[b]
Protein[a] -	966·1	781·7	0·809	4·4423	4·600	(5·683)
(Alcohol)[a] -	(1459·4)	(972·9)	(0·667)	(6·981)	(4·785)	(7·176)

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[a] The figures for O_2, CO_2, and Respiratory quotient result from the elementary constitution in starch, alcohol, and fat. (In animal fat, which is not a "chemical body," somewhat different values may be yielded for O_2, CO_2, Respiratory quotient, and Cal. O_2, according as one accepts differently the figures for the mean constitution in C, H, and O. Still, these can vary only about a few thousandth parts from the above.) The figures for these three substances are identical with those of Zuntz in *Pflüger's Archiv*, lxviii., p. 201. For protein, the calculation is more difficult. Here one must deduct from the elementary constitution of protein those quantities of C, H, O, N, and S, which, during its combustion, are passed ("excreted") in the urine and fæces. Only the residue which remains is available for the calculation of the "lung-respiration." As the amount of the "waste materials" in the urine and fæces varies; as, further, the elementary constitution and the caloric value of protein are stated differently by different authorities; as, again, the sulphur constituent of protein is taken into account by one observer and not by another, then the numbers for the same protein body (muscle-substance, for example) by the various observers differ greatly (Rubner,

Pflüger, Zuntz). Still more marked variations are found with different proteins. In the case of "muscle-substance," which, on the ground of association, was much used for obtaining standard values, the figures are lower for the above-mentioned values than for most other proteins, due, in fact, to the constituents of the extractives, which pass partly unchanged in the urine. In man, during prolonged hunger, but rarely is "muscle-substance" exclusively metabolized. This and other kinds of animal protein generally constitute the half of the metabolized protein, so that I have included for the above standard figures the mean of that value which Zuntz has calculated for "muscle-substance" and "casein" from the newest and most authentic estimations of his laboratory. (The work of Zuntz appears in the "Studies on the Metabolism of Man in High Altitudes." For calculations, etc., reference may be made to this work, and to his paper in *Pflüger's Archiv*, lxviii.)

These figures require further confirmation and renewed experiments, and I expressly emphasize that, for absolutely exact physiological purposes, average figures cannot be applied for the different proteins. The above figures for "protein" can, and ought, to serve only as approximate figures for conditions of average nourishment in man.

[b] According to Stohmann and Langbein, 1 gramme of animal fat develops 9,500 cal. From this the Cal. O_2 would be 4·705 and the Cal. CO_2 6·655.

Respiratory quotient and Cal. O_2 amount—

	R.Q.		*Cal. O_2 for 1 litre of O_2.*
in combustion of fat to	0·707		4·686
in combustion of starch to	1·000		5·047
A difference of	0·293	represents a difference of	0·361
A difference of	0·001	represents a difference of	0·00123

For every thousandth part increase of the respiratory quotient above the value of 0·707 the Cal. O_2 rises about 0·00123. Thus, a Cal. O_2 value of ($4·686 + x$ 0·00123) corresponds to a value of the respiratory quotient of ($0·707 + x$ 0·001). From this the following abbreviated table may be made for the oxidation of a mixture of fat and starch[1] [Schumburg and Zuntz (6) give an extensive table].

R.Q.	*Cal. Value of 1 litre O_2 (Cal. O_2)*	*Energy and O_2 need in per Cent.*	
		Carbohydrate.	*Fat.*
1·000	5·047	100	0
0·950	4·986	83	17
0·900	4·924	66	34
0·850	4·863	49	51
0·800	4·801	32	68
0·750	4·740	15	85
0·707	4·686	0	100

The calculation may be explained by an example from the work of Schumburg and Zuntz (7), in which, of course, somewhat varying figures were employed for the protein. Combined values are for one minute.

The excretion of nitrogen per minute amounted to 7·16 milligrammes, according to the daily average.

	C.c. O_2.	*C.c. CO_2.*	*Cal.*	*R.Q.*
From the total gas exchange =	252·59	211·17	—	0·836
Protein (7·16 × 6·25 milligrammes) =	43·42	34·43	194·3	—
Fat and carbohydrate .. .. =	209·17	176·74	—	0·845

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[1] See further on regarding the sources of error in the respiratory quotient in consequence of the excretion of carbonic acid by the skin.

With a respiratory quotient of 0·845 the caloric value of 1 c.c. of amounts to 4·856. Thus, 209·17 c.c. of O_2 from fat and carbohyd correspond to 1015·9 calories. There is thus a total of (194·3 + 1015·9 1210·2 calories formed per minute.

In this example the heat furnished from the consumed protein been placed separate in the calculation. This is certainly desirable the higher protein combustion. But still, the O_2 consumption gives approximately precise measure of the exchange of energy without co sidering the protein metabolism. From this comes the fact that caloric values of O_2 for the three chief food-stuffs do not lie very apart.

	Cal. O_2.	*Relative Proportion.*
For protein	4·600	100
For fat	4·686	101·9
For carbohydrate	5·047	109·7

They thus lie much closer to one another than Rubner (9) accepte on the ground of his researches (proportion according to Rubner = 100 109·0 : 118·6). The value for protein is lowest. This share in the exchange of energy is small, however, for omnivorous man. It is rarel under 10 per cent. or above 20 to 25 per cent. Should the latter happen —as, for example, at the height of digestion—with foods rich in protein, one would do well to pay attention to the nitrogenous excretion. In a fasting man at rest, one may take it that about 15 per cent. of the heat arises from protein. If now the remaining 85 per cent. be accredited to varying proportions of carbohydrates and fats, then the following relationships between the respiratory quotient and the caloric value of the oxygen result (based upon the same principles which underlie the previous table):

	The Oxygen is distributed			*The R.Q. amounts to*	*Caloric Value of 1 litre O_2.*	*Average.*	*Relative Value.*
	To Albumin.	*To Carbohydrate.*	*To Fat.*				
	Per Cent.	Per Cent.	Per Cent.				
I.	15	85	0	0·971	4·980	4·831	103·1
	15	78	7	0·950	4·954		102·6
	15	61	24	0·900	4·892		101·3
	15	44	41	0·950	4·831		100·0
	15	26	59	0·800	4·770		98·7
	15	9	76	0·750	4·708		97·4
	15	0	85	0·722	4·673		96·7
II.	10	0	90	0·717	4·677		96·8
	10	90	0	0·981	5·002		103·5
	30	0	70	0·738	4·660		96·5
	30	70	0	0·943	4·913		101·7

Thus, if the oxygen is correctly estimated, then a wrong value of the CO_2 to the extent of 6 per cent. is occasioned, and, in fact, a variation of the respiratory quotient amounting to 0·050, but only an error of 1·3 per cent. in the calculated amount of heat. Again, a greater or less share of the protein in exchange of energy, as was mentioned above, changes the caloric value of oxygen only insignificantly,[1] as follows from Part II. of the table.

Significance of the Zuntz Method.

The advantages of the Zuntz method are to be sought where the Pettenkofer method no longer quite applies, and *vice versa*. Its special advantage lies in the possibility to find almost constant end values, and to regard these as essential for the study of all the influences which act either for a short time mainly, or only for prolonged periods with varying intensity. Thus, a rise in the metabolism amounting to 15 to 20 per cent. in hourly researches is readily detected; but, on the other hand, they disappear in researches of a day's duration, because they lie within the error limits. A temporary investigation of different phenomena is only possible according to this procedure. The simultaneous estimation of the oxygen and the CO_2 teaches us to determine the respiratory quotients, and permits a recognition of the greater or smaller share during oxidation[2] taken by the various food-stuffs—fats, carbohydrate, alcohol, etc. The combustion of other assimilated materials (certain organic acids, glycerin, and so on) permit of being determined by this method, this not being feasible in the Pettenkofer procedure. We are indebted to the rapid method of Zuntz for the most valuable results regarding the height of the rise of metabolism during muscular work. Approximate figures may, indeed, be also found by the Pettenkofer procedure [Pettenkofer and Voit, Sondén and Tigerstedt, Wolpert, Johannson, etc.]. Still, a determination of the available physiological effect during the transformation of chemical energy into mechanical work may be attained in a complete manner only by the application of the principles which lie at the foundation of Zuntz's procedure.

Only in brief experiments is it possible to exclude all the factors which influence the gas exchange irregularly—namely, movement and administration of food. But as these factors powerfully influence the gas exchange unequally at different times, even to a moderate extent, it is desirable to exclude them as much as possible.

Certain sources of error, it is true, arise when, instead of the transformation of the food-stuffs resulting in end-products, certain intermediate bodies appear, which are temporarily stored in the body, or, as in diabetes, excreted from the organism. This has been recently discussed by Rubner (10) in the case of sugar formation from protein. Assuming that 70 grammes of glycogen (=78 grammes glucose) are derived from 100 grammes protein (an assumption that is scarcely ever realized in experiments on animals), Rubner calculates the caloric value of the carbohydrate-free residue of the proteid with 1 litre of oxygen as 3·1 calories (respiratory quotient = 0·4), and the carbohydrate part of the proteid as 5 (respiratory quotient = 1·0). More prolonged experiments —even those carried out over a period of twenty-four hours—are not absolutely free from similar errors of calculation.[1] They have also to be reckoned with in experiments of shorter duration—at least, under those conditions which are practically of most importance—namely, in the excretion of sugar from the organism. However, practically these are not of so great importance in the human subject as appears from the theoretical calculation, owing to the very moderate share taken by protein in the total energy exchanges.

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[1] Starting from calculations which primarily served other theoretical considerations, Erwin, Voit, and Krummacher (8) obtain figures which almost exactly accord with the above. (Cal. O_2 is reckoned from grammes of O_2 to c.c., and named C. by them—for proteid=4·698, for fats=4·677, and for carbohydrate=5·041.) The authors likewise accentuate the admissibility of calculating the formation of heat from the consumed oxygen. They refer to the fact that within the same kinds of groups of food mixtures (and waste products) this way of calculating heat offers far fewer sources of error than the employment of "mean combustion values."

[2] The presence of a normal respiratory mechanism is an assumption for this.

The errors are quantitatively much greater in the calculation of the amount of heat formed from oxygen absorption in the formation of fats from carbohydrates, a process which, in respect of the oxygen consumption, is exactly the antithesis of the sugar formation from protein. This transformation of carbohydrates into fat can assume immense proportions. For example, in Meissl's experiments on swine, 1,568 grammes starch were transformed into 948 grammes fat, carbonic acid being, of course, set free, and the remaining 620 grammes were, after taking up atmospheric oxygen, completely burned to their end-products. Under such conditions, the establishment of a caloric value for the oxygen and carbonic acid in short experiments is impracticable. But these conditions do not come into question to this extent in man on the usual diet or on a carbohydrate dietary.

Disadvantages of the Zuntz Method.

One disadvantage of this method lies in the employment of the mouth mask and the nasal clip, the application of which, as well as the maintenance of absolute rest, impose a certain constraint, and at the beginning also a slight degree of discomfort. Yet these discomforts are, after all, but slight, and easily overcome, as numerous personal experiments carried out by physicians have shown. The most important deficiency, as contrasted with Pettenkofer's method, consists in the impossibility of maintaining exact equilibrium for longer periods—for the whole day, or longer. It is impossible, by taking averages for the consumption during rest, digestion, and muscular work, to calculate exactly for a series of hours the actual daily exchange, and from this to deduce the food requirements of the organism and any excess that may remain in the form of deposited fat. Such calculations can and should only be regarded as approximate, furnishing merely what may be regarded as rough estimates of the probable daily exchange. Naturally, in numerous experiments one cannot dispense with such estimates, for in the consideration of many absolutely normal processes—*e.g.*, the work entailed in cycling, Alpine climbing, etc.—it is impossible to employ the Pettenkofer method. After emphasizing the advantages of the experiments of short duration by Zuntz's procedure, let it be distinctly understood that, especially in Rubner's hands, the protracted experiments have been of great service, although in our opinion the results obtained by them do not admit of such clear interpretation as in the case of those obtained by those of shorter duration. We are indebted to Rubner[1] for his numerous able researches, and the equally valuable conclusions which he has drawn from them with regard to the interchange of gases and the energy exchange of the organism. In the application of the different methods, success is by no means entirely dependent upon their general excellence, or upon any advantages they may respectively possess, but is quite as much—possibly more—dependent upon the care and insight of the experimenter. The two chief methods of indirect calorimetry have each their own value, the one supplementing the other. The lively controversy which was carried on some years ago with regard to the respective merits of the two methods has now died out, and present-day discussion usually deals rather with the special utilization of the results obtained in individual cases than with the principle of the method itself.

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[1] Thus, for example, on the first "hunger day" the amount of carbohydrate set free from the depot where it was stored, and then undergoing combustion, cannot be accurately determined, and therefore cannot be brought into the calculation. It is incorrect to calculate the CO_2 excretion as exclusively derived from the decomposition of proteid and fat.

Summary.

We may summarize as follows our view with regard to the relative merits of the methods of Pettenkofer and of Zuntz for the interpretation of the interchange of energy and matter. The experiments of twenty-four hours' duration are absolutely decisive, and afford a standard for the accurate measurement of the actual exchange within the day or within longer periods. It is from them alone that one becomes acquainted with the actual nutritive requirements, etc., and they now form the exact basis for the quantitative consideration both of the scientific and of the practical side of the question of nutrition. The method allows one to collectively summarize all the agencies influencing metabolism. On the other hand, it does not permit one to arrive at such a satisfactory determination of the effect of individual agencies. In cases which involve a sharply-defined separation and estimation of such influences, the experiments of shorter duration have a greater importance, and, in consequence of the simpler character of the technique, an incomparably greater field. This holds good especially in cases where the establishment of relatively small differences is involved.

In order to characterize the difference in the applicability of the two methods, we adduce two examples in which apparently the same or similar problems were investigated by the aid of the two methods. The one concerns the influence of age and sex, and in this case specially thorough researches are available, on the one hand by Sondén and Tigerstedt,[1] on the other by Magnus-Levy and Falk (11). The Swedish authors have carried out experiments upon the metabolism in children, adults, and the aged, when at rest (in every case in considerable numbers, in order to equalize individual differences). In their large respiration chamber we have to deal by no means with absolutely complete rest, but, in contrast to pronounced work, with a "rest" which allows of various activities throughout the day—namely, walking, reading, writing, playing, dressing, and undressing. This rest is, in addition, quite different in the case of a lively child of twelve or sixteen years, of a robust man not accustomed to indoor confinement, and of a man of eighty, who finds a passive existence the most comfortable. It is also quite different in the case of the two sexes. A troop of boys from fourteen to sixteen years of age enclosed in the Sondén respiration chamber perform quite a different amount of bodily movement from the same number of girls of the like age.

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[1] Recently Rubner's pupils have employed the Zuntz method in his laboratory, while, on the other hand, Zuntz has also carried out longer experiments in the same laboratory, where he had the opportunity of employing Pettenkofer's chamber and the apparatus of Reignault-Reiset.

Those researches show most clearly the different collective influence of age, sex, maturity, varying degrees of vitality and rest, as well as different states of mental excitability affecting secondarily the bodily condition. The practical requirement of an accurate knowledge of the actual metabolism under the natural conditions of age and sex is satisfied by means of such experiments extending over the twenty-four hours, as Tigerstedt rightly emphasizes in his well-known text-book. The numerical data of Magnus-Levy and Falk, which are much lower than those of the Swedish scientists, are more important, as Tigerstedt also tacitly admits, for determining the influence of age and sex on the metabolism necessary for the maintenance of life, etc. In every case, only single individuals in a condition of practical rest and in the fasting state were examined by Levy and Falk. All secondary influences such as are above indicated (the varying extent of movements, differences of temperature, etc.) were in this case absent, and the influence of age and sex, of weight and of size, remained alone recognisable.

A second example illustrates the influence of the respiratory and energy interchange.

The works of Zuntz (12) and his pupils have established with an almost physical accuracy the relation which the mechanical work carried out bears to the chemical energy expended for this purpose within the organism, not only in the human subject, but also in animals carrying out a variety of movements. These estimations have reached an accuracy which was not attained even in the careful experiments of Sondén and Tigerstedt. Pettenkofer and Voit, on the other hand, solved a question of quite another character in ascertaining the daily increase of the metabolism produced by bodily work, and the same statement holds good with regard to Wolpert's (12) researches upon the influence of industrial work on the excretion of carbon dioxide. Wolpert compared, in a number of workmen, the amount of CO_2 produced during periods of approximately four hours' duration while they were engaged in their customary occupations with the amount formed when they were resting. The latter consisted, however, in this case also by no means of entire abstinence from all movement, not even the rest obtained when lying comfortably on a sofa, but just a "sedentary occupation without work." The difference in the excretion of CO_2 during this "rest" and during the active work of the mechanics in Wolpert's research yields, therefore (like that in Pettenkofer and Voit's researches), not the total of the processes of oxidation expended in industrial work, but only the excess of the expenditure in mechanical labour over and above the energy metabolism of a person not occupied with purposeful manual labour in the true sense. The figures given by the Munich scientists, like those of Wolpert, are important, especially for the critical examination of the influence of practical working conditions; but they are quite different in type from the results of the researches of Zuntz's school. They can neither be compared nor brought into opposition with them.

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[1] The majority of these experiments lasted, it is true, only two hours. They were, however, carried out essentially under the same conditions as those of a day's duration performed in the respiration apparatus.

The application of the foregoing considerations to the study of other physiological conditions is obvious. The patients suffering from severe leuchæmia and diabetes, who were examined nearly forty years ago by Pettenkofer and Voit in their large apparatus, would undoubtedly behave otherwise as regards the extent of their movements, and would impose upon themselves greater restraint than the healthy individuals selected for comparison. It is scarcely permissible to come to a decision with regard to the indirect influence of pregnancy on respiratory interchange upon results obtained from experiments of twenty-four hours' duration. Farther, in what way could a bedridden patient suffering from phthisis accompanied by difficult respiration, one convalescent from typhoid, one suffering from diabetes, or, finally, one the subject of cardiac disease of such severity as scarcely to permit of movement in bed without resultant dyspnœa, be compared with healthy individuals in whom all these influences are absent? The actual nutritive requirements of such patients can obviously only be determined by means of experiments of twenty-four hours' duration, according to the method of Pettenkofer and Voit. The direct and immediate influence of the disease in itself can, however, be best ascertained in a simple and accurate manner by means of Zuntz's method.

The problem set before us in this physiological introduction to the pathology of metabolism is in the first place to separate all the distinct factors influencing respiratory interchange in the healthy subject. We shall only be enabled by the aid of such knowledge to come to a correct decision with regard to similar and other factors affecting respiratory interchange in pathological conditions.

For this reason we shall first consider the researches carried out by means of Zuntz's method. This procedure is also justified because Zuntz's technique has hitherto been chiefly applied to pathology, and we must therefore compare its results with those which are obtained in the case of healthy individuals by the same method.

Experiments of twenty-four hours' duration which inform us with regard to the actual food requirements in cases of disease are, with the exception of the isolated experiments of the Munich scientist, but few in number.[1] It should be explicitly stated that they are absolutely essential in order to render our knowledge more complete of the energy metabolism in disease. Such experiments will presumably be carried out to a larger extent in the course of the next ten years.

Analysis of the Energy Exchange of the Organism.

The transformation of energy may be analyzed into a fundamental exchange characteristic for the individual and an additional functional increment brought about by external and internal processes.

The fundamental energy metabolism becomes manifest in the most complete type of rest involving all organs (especially the muscular and digestive systems)—namely, in that minimal activity of the body which suffices for the maintenance of the normal functions during rest, and at the same time guarantees immediate readiness for the execution of all normal amounts of work (" fitness for work ").

This fundamental minimal metabolism has a different value in different individuals, and is dependent on variations in bodily constitution, of age, sex, etc.

It can vary in the same individual through external agencies, especially those of a climatic nature, through toxic influences, and through alterations in the composition of the body, which affect the extent of the normal functional activity, etc.

The functional increment is conditioned by the work done by the organs in so far as this exceeds the continuous minimal activity during rest.

With the view of giving a more convenient description, we deviate from this logical arrangement, and deal with the subject of the energy exchange in somewhat altered order as follows :

1. Preliminary note with regard to the respiratory quotients.
2. The normal minimum of metabolism (during absolute rest and during sleep).
3. The functional increment :

   Influence of different systems upon metabolism—

   (a) Of the digestive system (of food consumption).
   (b) Of muscular work.
   (c) Of the nervous and other systems (glandular, adipose and connective tissue, sexual, etc.).

4. Influence of various conditions upon the fundamental exchange :

   (a) Climatic conditions (light, sun, wind, moisture, heat, and geographical conditions).
   (b) Alterations of the respired air (O_2 and CO_2).
   (c) Toxic influences (see the work of Loewi in this book).

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[1] And very few others [Ebstein, Braunschweig, etc.].

5. Individual differences in the transformation of energy.

These are dependent upon—

(*a*) Size, weight, surface, composition, constitution, etc.
(*b*) Age and sex (and race).

6. Actual exchange and food requirements during the twenty-four hours.

The relations of the heat formation to heat dissipation, and the channels of heat loss, are dealt with in the section on Water.

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2. The Significance of the Respiratory Quotient.

Correct values for gaseous interchange and for the respiratory quotient can only be obtained by Zuntz's process when certain technical precautions are observed. At the beginning of each experiment (for a period of from three to ten minutes, varying with practice and with the capability of control on the part of the individual examined), ventilation is usually somewhat increased, and as a result of the greater activity of the respiratory musculature, the consumption of oxygen is somewhat raised above the amount consumed during rest. At the same time, as a result of the forced respiration, too much carbonic acid is withdrawn from the blood, and so the respiratory quotient is found to be too high. Subsequent to the period of forced respiration, there follows for some minutes one of quieter respiration, during which there is a compensatory diminution in the CO_2 output, below the amount that is formed, with the result that the respiratory quotient is too low. Only after these two periods are passed does the gaseous exchange become regular and the normal values for O_2, CO_2, and the respiratory quotient (v. Loewi, Katzenstein (1), and others) can be determined.

The respiratory quotient is affected by numerous other, frequently accidental, influences, apart from the purely mechanical ones associated with respiration, and so conclusions can only be drawn when the results obtained by numerous experiments are found to agree.

The values of the respiratory quotient—*i.e.*, the proportion of the O_2 intake to the O_2 output in the form of CO_2—

$$\left(\frac{\text{Gramme } O_2 \text{ in } CO_2}{\text{Gramme } O_2} = \frac{\text{c.c. } CO_2}{\text{c.c. } O_2}\right)$$

—on a fat or carbohydrate diet can easily be calculated from the elementary composition of these food principles. In the case of these two food-stuffs, decomposition products of different elementary composition, which would require to be taken into consideration, do not, as a rule, appear either in the urine or in the fæces in appreciable quantities. It is quite different in the case of protein, where the amounts of C, H, O, and S appearing in the urine and fæces must be deducted in order to ascertain the quantity of oxygen required for the formation of H_2O and CO_2. As its amount varies in different experiments, and as the nature of the calculation differs not only for different proteins, but also as carried out by different authors, so the statements vary as to the amount of oxygen requisite for the combustion of the proteid, and also as to the amount of CO_2 expired. For these reasons the respiratory quotient, as well as the physiological and physical heat values, vary in the case of a protein dietary.

The amount of the respiratory quotient for the following substances is as follows :

Starch, etc.	1·00
Fat	0·707
Protein	0·809
Alcohol	0·667

The calculated theoretical limiting values of the respiratory quotient in the case of the exclusive combustion of the carbohydrates, or of fats, are usually not attained within the organism, since proteid is invariably oxidized along with these bodies. If we take for the fasting state (the individual being in fair average condition) the proportion on the part of the proteid in the total energy exchange of the organism as 15 per cent. of the latter, then the limiting values of the respiratory quotient, with a distribution of the energy exchange, are as follows :

With 15 per cent. (energy value) protein + 85 per cent. (energy value) carbohydrate = 0·971 respiratory quotient.

With 15 per cent. (energy value) protein + 85 per cent. (energy value) fat = 0·722 respiratory quotient.

Under normal nutritive conditions these values neither rise above this level nor fall below it, provided that the oxidation of the food-stuffs to their end-products is complete, and that no intermediate products appear.

If the experimental technique be correct, and the analysis accurate, the height of the respiratory quotient gives us an idea as to the nature of the bodies which have undergone metabolism in the organism.

Although practically all the oxygen is taken in by the lungs, a portion of the CO_2 which is formed in the body leaves by the skin, and so is not calculated by Zuntz's method. According to Schierbeck and Willebrand, about 7·2 to 9·0 grammes are excreted daily by this channel, or 2½ to 3 c.c. per minute at atmospheric temperatures below 32°, or, in other words, about 1½ per cent. of the 200 c.c. CO_2 excreted during a period of rest.[1] The respiratory quotient is, therefore, by exclusive examination of the pulmonary respiration, always found to be about 0·010 to 0·015 lower than would be reckoned from the following theoretical calculation.

During fasting the respiratory quotient is, as a rule, low—about 0·8, and also below that value; still, in many experiments, even in the early hours of fasting, values up to 0·9 and over have been observed. In such cases there is, either as a result of a preceding diet rich in carbohydrates, a large amount of sugar in the circulation, or the reservoirs for carbohydrate are fully stored; or, on the other hand, in these individuals the oxidation of the sugars has taken place more regularly during the whole day than is usually the case. One must not, without further evidence, draw the conclusion, as in some cases has been done, that the high respiratory quotient in the fasting condition is due to an insufficient oxygen intake. One may only draw such a conclusion if on other evidence an insufficiency is undoubtedly proved—*e.g.*, in excessive muscular work.

The course of the respiratory quotient has thus given information as to the rapidity with which carbohydrate and other bodies introduced into the alimentary canal or blood have undergone metabolism. (For further information as to the significance of carbohydrates and other food-stuffs as sources of muscle energy, see later.) The combustion of alcohol (respiratory quotient 0·667) may be shown, just as that of the organic acids, from the fall in the respiratory quotient. A departure of the respiratory quotient values from the above-mentioned limits only occurs (excluding cases in which respiration is abnormal or insufficient) in cases where, along with the combustion to the end-products, there have been other metabolic changes, such as, *e.g.*, the formation of a body poor in oxygen from one rich in that element (fat from sugar), or, on the other hand, one rich in oxygen from one poor in the same—*e.g.*, sugar from proteid or fat.

In the formation of fat from sugar, large quantities of CO_2 are set free without oxygen intake from the air (from 100 grammes starch, furnishing about 42 grammes fat, approximately 45 grammes CO_2 are set free). In such a case the respiratory quotient may rise to 1·38 [Bleibtreu (4)]. On the other hand, the respiratory quotient falls in the formation of sugar from proteid, for which a considerable oxygen intake is necessary without corresponding quantities of CO_2 being expired, if the glucose formed is either stored as glycogen or is excreted in the urine. I have reckoned that the respiratory quotient of the carbohydrate-free residue of the protein[1]—*i.e.*, the residue remaining after the formation of 60 grammes glucose from 100 grammes protein—is 0·613 (5).

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[1] The amount is twice as great in the horse (Zuntz and Hagemann).

If a diabetic patient subsist exclusively on this carbohydrate-free proteid residue and fat, the respiratory quotient must lie between 0·613 and 0·707. As in these cases the fat is more largely involved in the oxidation than the proteid, the respiratory quotient must always be slightly above 0·68, even if the excretion of certain O_2 rich bodies of high respiratory quotient, such as oxybutyric acid, has also to be reckoned with. It is only in the case of an exclusive proteid predominance of the metabolism, as after phloridzin and at the height of digestion, or in the case of sugar formation from fat, that the respiratory quotient sinks still lower without, however, falling below 0·62 [Magnus Levy].

If we exclude fat formation from carbohydrate, sugar from proteid (possibly also from fat), and the excretion of bodies like acetone, we know of no other transformations (formation of intermediate bodies) which can appreciably alter the respiratory quotient.

It is true that in the organism there frequently occurs an O_2 storage, or a carriage of O_2 from highly to less highly oxidized substances, or *vice versa*—as, for example, in respiration of gas mixtures rich in O_2 or in glycuronic acid formation from sugar. Here also, however, as in other anomalies in metabolism where intermediate products (amino-acids, aromatic and fatty bodies) appear unoxidized in the urine, there are only proportionately small quantities of O_2 fixed and again given off in the changes accompanying the formation of those intermediate products. In contrast to the formation of sugar from proteid, and fat from sugar, these processes in the course of twenty-four hours only reach the value of a few grammes, and this can affect but temporarily the respiratory quotient, only diminishing it to an infinitesimal extent [Magnus-Levy (4)].

Such respiratory quotients as 0·6, and even 0·5, quoted in French literature as occurring in health or disease, must be regarded as incorrect, and due to error of some sort or other. Incorrect experimental detail, or faulty analysis, especially in the determination of the oxygen, may furnish the explanation. If an explanation of such divergent values is given by referring to some intermediate products formed during meta-

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[1] I am fully conscious of the inaccuracy of the expression. This residue has no existence as a positive quantity in the calculation. After subtraction of the elements of the protein excreted in urine and fæces, there are contained in—

	C.	*H.*	*O.*
100 grammes protein	38·6	4·24	9·24
60 „ sugar	24·0	4·0	32
Residue	+ 14·6	+ ·24	− 22·8

Therefore, in this formation of sugar a considerable quantity of oxygen must be taken up from the atmosphere (22·8 grammes).

Gm.		O_2. Gm.		CO_2. Gm.
14·6	C require	38·9	and form	53·5
0·24	H „	1·92	„	2·16 H_2O
	Plus the above	22·8		

Total required 63·6 O_2. R.Q. $= \frac{38·9}{63·6} = 0·613$

bolism other than those referred to in the preceding remarks, one must carefully analyze each case, and calculate whether the results obtained can be explained from the extent of such an altered metabolism.

Even in the case of the extremely low respiratory quotient (0·5 and less) observed by different investigators for the hibernating marmot, the known intermediate metabolic changes do not furnish a satisfactory explanation. If the estimation of the O_2 in such investigations where the Reignault-Reiset apparatus has been employed is not incorrect (Durig and Zuntz have drawn attention to the possibility of errors, these being especially great in the case of hibernating animals, where the amount of oxygen used up is so small), and if alterations in respiration do not play a part, one must look in this case for new and unknown metabolic processes. Before, however, such processes can be proved to play such an important rôle in the case of abnormally low respiratory quotients in man, one must have some other evidence beyond that obtained by investigating the changes which occur in hibernating marmots, as the metabolism in the latter is brought down to an extremely small fraction of the normal.[1]

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[1] If, on the other hand, the low respiratory quotient in hibernation be explained by the sugar formation from fat and the accumulation of the former in the organism (and this possibility does not appear to be excluded), one must be clear as to the extent of this process. It is easy to calculate how much fat must be changed into glycogen in order that such low respiratory quotients as 0·5 and 0·33 may be obtained. If we take for calculation the most favourable case where only fat is metabolized (not from proteid or carbohydrate), and also, which appears quite as improbable, where all the carbon of the fat is changed into the carbon of glycogen, then 100 grammes fat with 84 grammes O_2 (58·8 litres O_2) = 172·3 grammes glycogen + 11·7 grammes H_2O, as the following calculation shows :

		C.	*H.*	*O.*		*H_2O.*
100 grammes glycogen	=	44·4	6·2	49·4		
100 grammes fat	=	76·5	11·9	11·5		
172·3 grammes glycogen	=	76·5	10·6	85·1		
Difference ..	..	0	+1·3	−73·6		
1·3 grammes H require	..	..	..	.. 10·4	=	11·7
Total required	..	..	..	.. **84**	=	58·8 litres O_2

Now,	*Require Litres O_2.*	*Give Litres CO_2.*
100 grammes fat for complete combustion	201·9	142·7
x 100 grammes fat for complete transformation into glycogen	x 58·8	0
100 + x 100 grammes fat	201·9 + x 58·8	142·7

If, in the equation—

$$\frac{142{\cdot}7\ CO_2}{201{\cdot}9 + x\ 58{\cdot}8\ O_2} = \text{respiratory quotient the respiratory quotient shall amount to } 0{\cdot}5 \text{ or } 0{\cdot}33,$$

then there must have been in the first case, in addition to 100 parts of combustible fat, 142 parts fat transformed into 244·6 grammes glycogen ; in the second case 385 grammes fat changed into 666·5 parts of glycogen. A transformation to this extent will not be accepted even by the upholders of that theory of diabetes. If, as Seegen believes, the fat is burned as sugar, then naturally the O_2 intake and the respiratory quotient (*in toto*—*i.e.*, if fat-sugar and sugar-free residue of fat undergo combustion together) must be quite as high as when the fat is directly consumed without the formation of intermediate bodies. A decrease in the respiratory quotient can only, then, occur when the sugar formed from proteid or fat is temporarily (by glycogen storage) or permanently (by excretion) prevented from undergoing combustion.

amounted in the case of Johannson in a state of hunger (weight 73 kilogrammes) to 20·7, 24·8, and 33·1 grammes respectively, Taking the excretion in the first state of rest as 100, the amounts during the second and third would be 120 and 159 respectively; or, taking the third as 100, the first and second would be 63 and 76 respectively. This agrees, on the whole, with the differences which are found to exist, on the one hand, between the results of Magnus-Levy, Falk, and Johannson in the case of "prescribed" rest and, on the other hand, with the figures of the majority of other scientists.

Energy Exchange during Sleep.

Low numbers, similar to those during prescribed muscular rest, are found during quiet sleep. A. Loewy (7) and Magnus-Levy (6) found that the consumption of oxygen sank only 1 to 6 per cent. both in sleep due to the administration of morphine and in natural sleep. The work done by the respiratory muscles and the heart was in this case even less during sleep, and the muscular rest in the waking condition not so complete, as in the case of Johannson, who attained in his experiments upon himself a condition of muscular relaxation of such uniform character as was scarcely reached by any other investigator.

He found in his experiments of one to two hours' duration an excretion of 20·72 grammes carbon dioxide per hour in a state of complete muscular rest, in the experiments during sleep an increase of 1 per cent. (the latter arising from slight movements prescribed by the experiment) (9). By combining the results obtained during periods of two hours, each selected from different sections of separate days, he found the exchange of CO_2 during the night to be 96·3 per cent., that during the first eight hours of the day = 103·5 per cent., and that during the second eight hours of the day = 100·1 per cent. of the daily average. The CO_2 excretion in the case of the dog, as Rubner (10) demonstrated years ago, is not essentially different during sleep and waking while the animal is in a condition of true rest.

For the estimation of the minimal metabolism during complete rest, we are therefore justified in taking into consideration the respiratory interchange of gases during sleep, as well as in the waking state during a condition of absolute rest[1] (*cf.* the section on Individual Variations of the Minimal Metabolism).

A large proportion of the processes of oxidation, and of heat formation during rest, takes place, without doubt, within the relaxed muscular system. Up to the present time the researches of Zuntz and Roehrig have been regarded as confirming this statement. According to these experiments, curare was found to decrease the exchange of gases in animals to the extent of 30 to 40 per cent., and this decrease was due chiefly to a diminution of muscular tone. It must be conceded that this conclusion is not correct. The rabbits in these experiments were apparently not in a condition of complete muscular rest prior to the action of the curare. If the exchange be ascertained for the unpoisoned condition, with the exclusion of all voluntary movement, curare causes no diminution, according to Frank and Fr. Voit. Notwithstanding this, the supposition remains certain that even during rest the greatest proportion of exchange occurs within the muscles (11).

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[1] *Comparison of Exchanges during Day and Night.*—A comparison of the interchange of gases during the night with the actual exchange during the day while occupied with the customary work involves a question of a somewhat different nature. In the case of such a comparison, the exchange is naturally higher in the waking condition. Pettenkofer and Voit, who not quite fitly contrasted a period of twelve hours during the day with the same period of time during the night (the latter not entirely devoted to sleep), found a relation of [illegible] to [illegible], or an average [illegible] for the CO_2 excretion during day and night respectively. It is more accurate to compare the excretion for the number of hours actually spent in sleep (six to eight) with that during the same period in the waking condition. Sondén and Tigerstedt (13) found a relation of [illegible] to [illegible], or an average of [illegible], and I personally have calculated smaller quotients from the data of numerous other experiments on metabolism during "rest" furnished by Swedish and American scientists.

The course of the day is without direct influence upon the interchange of gases and upon heat production (Rubner for CO_2 in the case of the dog, Magnus-Levy for O_2 and CO_2 in the case of the human subject, Smith and Johannson for the CO_2, also in the case of man). The daily variations amount only to a small percentage, and these very slight deviations arise (like the very small differences of body temperature observed under the same conditions of hunger and absolute muscular rest) from slight external influences—*e.g.*, light, etc., abnormal physical and psychical stimuli—which cannot be entirely excluded, and which somewhat disturb, by means of their respiratory, cardiac, and muscular reflexes, the uniform resting condition of all the organs (14).

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4. The Functional Increment: Influence of the Different Systems on the Interchange of Energy.

(a) INFLUENCE OF THE DIGESTIVE SYSTEM—THE FOOD CONSUMPTION.

Influence of Food Consumption upon the Respiratory Interchange of Gases.

In every case an increase of the respiratory interchange follows the taking of nutriment. This increase varies in extent in the case of different food-stuffs, and is in part so small as frequently not to be detectable in experiments of a day's duration. This statement holds good in the case of animals (the dog), in which this increase cannot be detected. When sufficient diet is taken (within the bounds of chemical heat regulation), by means of a corresponding limitation of muscular metabolism, a chemical regulation, in the sense assumed by Rubner to hold good for animals, appears to be non-existent in the case of the human subject. In the latter case the increase of metabolism after the taking of food always makes itself distinctly perceptible upon the results of experiments lasting for one hour. On the other hand, experiments of a day's duration are unfitted—at all events, in the case of man—for the estimation of the action of food consumption in increasing the processes of oxidation. In the case of man, the other numerous and often more marked actions upon respiratory interchange cannot be excluded or quite equalized in experiments of such duration.

The action of food consumption upon the interchange of gases in the human subject has disappeared, as a rule, some twelve hours after a meal of ordinary size. This time was selected by Rubner as the starting-point for his researches.

Extent of the Rise in Metabolism following Consumption of Food.

The increase in the consumption of oxygen and in heat formation is least after taking fat, larger in the case of carbohydrates, and greatest in the case of a proteid diet. This statement is true at least for the first ten hours, concerning which continued experiments [Magnus-Levy (2)] are available. The majority of other workers found the same sequence as regards the extent of the influence exerted on the gaseous interchange. Rubner alone, as the result of observations of twenty-four hours' duration, carried out upon the dog, has recently ascribed a more marked action to fats than to carbohydrates. This result may possibly be explained by the facts that the digestion of fats is not completed within the first ten hours, and that the percentage increase of metabolism, although less in itself, lasts longer.

The conditions in the human subject may be rendered clear by means of the following observations in which the gaseous interchange was traced hour by hour [Magnus-Levy]:

Consumption.	*Fasting Value* (*c.c.* O_2).	*Percentage Increase of the* O_2 *Consumption.*							
		Hour after Meal—							
		1st.	2nd.	3rd.	4th.	5th.	6th.	7th.	8th.
310 gms. roast beef (weighed after being cooked) ..	230·8	12	13	15	20½	20½	14		20½
210 gms. bacon ..	226·4	1	4½	4½	5½	6	6	9	9½
280 gms. white bread	219·1	+33	—	+32	+4		+3	+12½	+11½

Consumption.	*Fasting Value.*	*Variation in the Respiratory Quotient.*							
		Hour after Meal—							
		1st.	2nd.	3rd.	4th.	5th.	6th.	7th.	8th.
250 gms. beef ..	0·76	0·76	0·77	0·79	0·78	0·73	0·77	0·74	—
210 gms. bacon..	0·78	0·72	0·75	0·75	0·72	0·74	0·74	0·73	0 70
295 gms. white bread	0·72	0·82	—	0·86	0·90	—	0·90	0·87	—

The different food materials taken during these experiments had admittedly different caloric values, the bacon having the highest value, the roast beef the lowest. The rise or fall of the respiratory quotient shows distinctly the share taken in the combustion by the different food-stuffs.

The great increase in the quantity of oxygen absorbed after the consumption of meat is not dependent upon extractives. Meat which has been macerated and vegetable protein are no whit inferior to fresh meat in their action [Magnus-Levy]. The increased respiratory exchange depends not so much upon the digestibility of the food as upon its effect upon metabolism [Magnus-Levy, Pembrey, and Spriggs, etc.].

All nutrient materials and mixtures of food-stuffs (amongst others, the following were examined : milk, cane-sugar, glucose, vegetable protein, beer, vegetables, etc.) increase the gaseous interchange in proportion to the nature and amount of the material contained in them. Water only does so when taken cold and in large quantities. Under these conditions it produces this effect on account of its stimulating action. Under other conditions it is without influence (see Dapper in this book). The same statement holds good for coffee, except in great concentration (see A. Loewy's discussion in this book). For references to alcohol, see the corresponding section of this work.

The following numbers — averages of three experiments — were observed on a mixed diet sufficient for maintenance and with an energy value of about 2,400 to 2,500 calories [Magnus-Levy (2)] :

Fasting Value Early in the Morning.	*Percentage Increase of the O_2 Consumption.*								
	Hour—								
	1st.	2nd.	3rd.	4th.	5th.	6th.	7th.	8th.	
217·4 c.c. O_2 ..	27	27	16	6	—	—	—	—	After breakfast
	40	35	27	19	17	9	—	—	„ midday meal
	33	23	12	6	—1	—	—	—5	„ evening meal

The gaseous interchange during these experiments was raised most markedly in the first two hours. The increase had died away four to five hours after breakfast and after the evening meal respectively, and within six to eight hours after the midday meal. In the period after midnight no further increase occurred in the consumption of oxygen. The respiratory quotient was almost invariably raised (about $\frac{3}{100}$ to $\frac{7}{100}$ and more), as compared with its original value, in consequence of an increased combustion of carbohydrates. The quantity of carbon dioxide, therefore, increases more markedly than the oxygen.

The total augmentation of the quantity of oxygen utilized amounted in the fourteen hours of actual digestion to 21 per cent. of that absorbed during the minimal metabolism of the resting organism. The average increase, calculated for the twenty-four hours, amounted to 13 per cent. in the case of oxygen, 20 per cent. in the case of carbon dioxide, and 15 per cent. for heat formation. In this case an additional quantity of oxygen, amounting to 40 litres, was consumed during the day in order to utilize these food materials. This increased consumption of oxygen corresponds to a heat formation of 190 to 200 calories, or about 8 per cent. of the energy contained in the food taken. These are average numbers. The gaseous interchange was temporarily greater in many of the earlier experiments [Smith, Speck, and others]; in other experiments it was less distinctly increased. The figures vary even in the case of the same individual [Koraen, Jaquet, and Stachelin (3 and 4)]. Consequently, it is not permissible to draw far-reaching conclusions from isolated experiments. In order to compare the effect of food consumption in different individuals, one must give dietaries having the same composition and the same caloric values, and one must take into account the absolute as well as the percentage increase of exchange. We shall certainly not err if we estimate the rise in daily metabolism consequent upon a sufficient diet at approximately 10 to 15 per cent. of the minimum metabolic interchange in the quiescent organism (*Grundumsatz*).

The increase may become much greater if excessive quantities of food be taken. The influence of such diet has been studied by Rubner in many experiments. A diet consisting exclusively of protein produces by far the most pronounced effect. The heat produced by a large dog during the twenty-four hours was observed by Rubner (1) to rise 42 to 46 per cent. after the consumption of 2,000 grammes of meat. At the height of digestion the increase is still greater. Under conditions of exactly the same nature it amounted to 88 to 93 per cent. during the fourth to the seventh hours of digestion [Magnus-Levy (2)]. Excessive supplies of fats or carbohydrates have a less energetic action than equivalent quantities of protein.

Even in the human subject an increase of metabolism bears a certain proportion to the amount of food supplied to the organism (examples in the papers of Magnus-Levy).

It follows that no kind of food can be supplied to the organism without work and expenditure. The consumption and utilization of food-stuffs claim a small, although varying, proportion of the energy contained in them. If muscular work be carried out during digestion, the augmentation of heat interchange is the arithmetical sum of the quantities of heat derived from the two processes [Johansson and Koraen (5)]. Consequently, the formation of heat occurring in other organs cannot be transformed into mechanical energy within the muscles.

Svenson (6) found approximately the same increase of gaseous interchange after meals in the case of patients convalescent from pneumonia, as Magnus-Levy had found in healthy individuals. He found a somewhat greater increase than normal in the case of patients suffering from enteric fever. According to Jaquet and Svenson (6), individuals suffering from obesity appear to respond to the influence of food consumption with a less marked increase of the processes of combustion than healthy individuals. Yet it must be admitted that the method of calculation adopted by the Swedish scientists was apparently erroneous [Magnus-Levy (6)] (*cf.* the chapter on Obesity, Vol. II.).

Significance of the Increased Metabolism following the Consumption of Food.

Different explanations have been offered for the increased metabolism following the consumption of food. Speck, Zuntz, Mering, and Magnus-Levy (7) ascribe the increase mainly to intestinal and glandular work—that is, to the expenditure required for the enlarged demands upon the muscular system, and for the work of secretion carried out by the numerous glands present in the alimentary canal. The augmentation of cardiac and respiratory activity also involves an increased absorption of oxygen. It must be admitted that this view does not afford a satisfactory explanation of the extraordinary increase of metabolism resulting from an excessive protein diet. For this reason Magnus-Levy, who in this respect agrees with Rubner, has assumed, in addition to the glandular work proper, a specific action on metabolism produced by the excess of protein. In opposition to the foregoing theory, Rubner has ascribed little significance to glandular work proper in the wider sense, and has referred the increased metabolism essentially to processes carried out by the organism as a whole with the object of utilizing the nutriment. Fick, Jaquet and Svenson, and Koraen (7) followed Rubner's view. Every food-stuff possesses, according to Rubner, a "specific dynamic" action. He assumes that the protein molecule becomes decomposed in all cases into a nitrogenous component, and a non-nitrogenous component of carbohydrate nature. According to this theory, the organism is unable to utilize for its maintenance the heat derived from the combustion of the former constituent, as distinguished from that resulting from other types of combustion. According to his view, out of the total 26 calories that are set free within the body as a result of the metabolism of 1 gramme of nitrogen, only 18·6 calories can be actually utilized—that is to say, can replace the energy otherwise derived from other sources. The remaining 7 calories are "surplus" heat, and mainly dependent upon thermochemical processes which accompany the decomposition of the protein molecule. Thus the 18·6 calories, which are yielded by 6·25 grammes of proteid (containing 1 gramme of nitrogen) in the form of available heat, correspond to about 4·4 grammes of glycogen, which are derivable from 6·25 grammes of protein. Further, the carbohydrate radicle split off from the protein is the true source of the energy present in the protein molecule. The energy derivable from the nitrogenous component plays no part as a source of energy for the organism, but leaves it unused without lessening the expenditure of other forms of energy. A specific heat formation is also assumed by Rubner to occur after the consumption of carbohydrates and fats, and similar secondary thermo-chemical processes are adduced as its cause.[1]

According to Rubner—his train of thought recalls that of Liebig in some respects—the organism can utilize for the following purposes the potential energy brought to it:

1. For simple heat formation.
2. For the special movements of matter which constitute life, and which, after passing through this form of energy, are converted into heat. Heat—that is, undoubtedly, the heat derived from without, as well as that resulting from concomitant thermo-chemical processes—cannot maintain life.

We recognise a specific action of protein nutriment without adopting Rubner's explanation, which leads to contradictions when applied in detail. We believe, however, that the increased oxidation occurring after the consumption of fats and carbohydrates, as well as that following the consumption of protein, are to be referred mainly to the intestinal and glandular work proper. Numerous reasons favouring this view have been brought forward by Speck, Mering, and Zuntz, J. Munk, A. Loewy (8), Magnus-Levy (bone-feeding), and others, and although theoretical and arithmetical objections might be raised to many of these investigations, yet a critical review of all the researches favours the explanation given by Zuntz and Mering.[2]

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[1] The decision of the foregoing question will become easy as soon as we have obtained a solution of the chemical problem dealing with the formation of sugar from protein. If, as we believe, the derivation of sugar from protein involves the detachment of nitrogen in the form of ammonia, and not in combination with a carbon chain, then Rubner's theory, which is also open to other objections, will prove difficult to maintain. The following objection may also be raised against it—that, even if a decomposition of the protein molecule into a non-nitrogenous and a nitrogenous component does occur, sugar is not, as a rule, derived from the former.

[2] Thus intestinal reflexes cannot be entirely excluded in the case of stimulation of the intestine by means of saline purgatives [A. Loewy]. The experiments of Nehring

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(b) Influence of Muscular Work on the Transformation of Energy.

Differences in the nature of the work done—Useful effects—Dependence of the expenditure of energy and of the useful effects upon secondary influences—Cardiac and respiratory work—Therapeutical applications.

(a) *Some General Considerations.*

The marked influence exercised by muscular work upon metabolic changes involving matter and energy, which was first valued at its true worth by Lavoisier, has afforded a subject of study for many authors—*e.g.*, Smith, Pettenkofer and Voit, Speck, Hanriot and Richet, and many others. Yet it is only within recent times that the relation between the amount of work done and the expenditure of energy required for its performance has been established with accuracy. At the present time our knowledge is founded chiefly upon researches by N. Zuntz and his pupils, along with those carried out in the laboratories at Stockholm and Berne. They have not only made clear the relations between work and metabolic changes in matter, but also rendered possible the accurate estimation of the increase of metabolism occurring in all those varieties of functional work that interest the physician. The researches were carried out on horses and dogs, as well as upon the human subject, with every possible variation in the experimental conditions—*e.g.*, for walking on the level as well as for climbing, with and without loads, for cycling and swimming, for statical work, such as that involved in winch-turning

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and Schmoll upon the action of rice in cases of diabetes do not satisfactorily demonstrate the point as the authors assume, since rice contains approximately as much proteid as the animal food given in the control experiments.

under certain conditions, and also for the drawing of loads in the case of animals. The amount of oxygen consumed during work (after deduction of the consumption during rest) is to be regarded as a measure of the expenditure of energy. After taking the caloric factor into account, the amount of heat transformed and its mechanical equivalent can be readily calculated from the amount of oxygen consumed.

The researches have been mainly carried out with the aid of a rotating treadwheel, upon which the individual under observation remains fixed in position. To a less extent the experiments have been performed in the open. In the latter case, the individuals concerned carried the respiration apparatus on their backs. The investigation of the work done during walking and climbing proved specially applicable both for practical measurement and for theoretical consideration, inasmuch as the expenditure of energy in raising the body when climbing (*i.e.*, in carrying out effective and useful work) can be accurately determined from a combination of the results so obtained. These forms of work also, as a matter of fact, are of main importance in actual life.

(β) *Mechanics of Respiration.*

The quantity of air respired is increased during all types of work in order to overtake the increased oxygen requirements and the augmented formation of carbon dioxide. If it amounts to 4 to 7 litres in the adult man while at rest, then there pass through the lungs per minute 10 to 15 litres during moderate work, 20 to 25 litres during fairly heavy work, and 33 to 38 litres during arduous labour. During swimming the quantity may rise as high as 50 litres [Kolmer (1)]. While the gaseous exchange within the lungs reaches, during severe work, five to seven times its value, during rest the concomitant consumption of oxygen and excretion of carbon dioxide increase seven to ten times their value at rest. Thus, for example, L. Zuntz (1) consumed 1,442 c.c. of oxygen per minute when cycling at a speed of 5 kilometres per hour, 2,307 c.c. at a speed of 21 kilometres per hour. He consumed 1,230 c.c. of O_2 per minute during rapid walking (6 kilometres in the hour), and when running (8·4 kilometres per hour) 2,552 c.c.—*i.e.*, five to ten times his requirements of 236 to 263 c.c. O_2 during rest. Since the rise in the quantity of oxygen consumed surpasses, as a rule, the increase in the extent of ventilation, the utilization of the inspired air must consequently be increased. For example, ventilation and oxygen deficit amounted to:

		Ventilation.	*O_2 Deficit.*
L. Zuntz	resting	5·5 litres.	5·38 per cent.
,,	walking on the level	16 to 22 litres.	3·7 to 4·85 per cent.
,,	climbing up a steep gradient ..	25 to 28 ,,	6·5 to 7·5 ,,
N. Zuntz	resting	5 litres.	5·17 per cent.
,,	climbing up a moderate gradient ..	15·2 ,,	6·04 ,,
,,	climbing up a steep gradient ..	26·0 ,,	6·40 ,,

It is interesting to note that the extent of ventilation and the absorption of oxygen can reach much higher values in the horse, the organism of which is best fitted for running, than in man—namely, twenty times their resting value [Zuntz and Hagemann (1)].

Consumption	during rest	34 litres respired air,	1·48 to 1·65 litres CO_2 per minute.
,,	,, moderate work	300 ,, ,,	12 to 14 ,, ,,
,,	,, hard work ..	500 ,, ,,	19 to 29 ,, ,,

The foregoing maximal performances in gaseous exchange, which have been measured in the case of human beings and animals, represent by no means their maximal functional capabilities. The above-stated figures are, without doubt, far exceeded in the case of athletic efforts, such as those which occur in competitive running, racing, etc.

The ventilation is increased not only by acceleration, but to an even greater extent by deepening of the respirations.

	Number of the Respirations.	*Depth of the Respirations.*	
During rest	13	470	Schumburg and Zuntz (1).
On the march	20 to 22	900 to 1,500	
During rest	6	800	Leo Zuntz (1).
„ fairly rapid walking and cycling ..	11 to 14	2,380 to 3,000	

(γ) *Consumption of Oxygen and Expenditure of Energy in the Case of Different Types of Movement—e.g., during Walking, Climbing, and during the Work entailed by Rotating a Wheel.*

The following example illustrates the mode of experiment and the nature of the calculations :

CALCULATION OF THE CONSUMPTION OF OXYGEN FOR THE UNIT OF WORK DONE DURING WALKING ON THE LEVEL AND DURING CLIMBING [KATZENSTEIN (2)]. THE VALUES ARE CALCULATED PER MINUTE.

Character of the Work.	*O_2 Consumption in c.c.—*			*R. Q.*	*Horizontal Distance.*	*Ascent.*	*Weight of the Clothed Individual.*
	Sum Total.	After Deduction of the Resting Value.					
		Sum Total.	For each Kg. moved.				
					Metres.	Metres.	
1. Rest	263·75	—	—	0·801	—	—	55·53 kg.
2. Walking on the level with minimal incline ..	763·00	499·25	8·9906	0·805	74·48	0·581	
3. Exercise on an incline equivalent to a 10·8 per cent. rise ..	1253·2	989·45	17·819	0·801	67·42	7·270	

Let x be the O_2 consumption for the movement of 1 kilogramme over a horizontal distance of 1 metre.

Let y be the O_2 consumption for lifting 1 kilogramme through a vertical distance of 1 metre.

From row 2 of the table it follows that $74·48\,x+0·581\,y=8·9906$ c.c. O_2.
From row 3 of the table it follows that $67·42\,x+7·270\,y=17·819$ c.c. O_2.

$$\therefore\ x=0·1095 \text{ c.c. } O_2$$
$$y=1·4353 \text{ c.c. } O_2.$$

If the respiratory quotient be 0·803, then 1 c.c. O_2 has a caloric value of 4·792, and corresponds to 2·037 metre-kilogrammes.

Thus the movement of this particular individual horizontally over 1 metre caused a consumption of energy of 0·1095 × 2·037 = 0·223 metre-kilogrammes per kilogramme, while the movement upwards called for a consumption of 1·4353 × 2·037 = 2·924 metre-kilogrammes per kilogramme.

After-effect of Work.—In calculating the amount of work expended, the fact has to be taken into consideration that the increased ventilation and gaseous metabolism do not at once return to the normal immediately after the completion of the work. The extent of this after-effect of work depends mainly on the amount of work done. A. Loewy (2) found that the ventilation returned to the normal within four to nine minutes after medium work, and in twenty minutes after fatiguing work. The consumption of oxygen ran parallel with the ventilation. The latter was raised 8 to 9 per cent. above normal within six minutes after medium work, calories 24 to 32 per cent. above normal within ten minutes after severe work. After a further ten minutes the additional rise was slight. This increased consumption, which depends upon the amount of work done, but survives its actual performance, mut be taken into consideration in all accurate experiments [see also Speck (2)].

The expenditure for work becomes added in its entirety to the extent of metabolism during rest or during minimal metabolism. If any muscles pass into a state of activity, neither the heat developed by these groups of muscles during their resting condition, nor the metabolism of other resting organs, is diminished in order to assist in supplying the heat developed by them during the performance of work.[1] The proof of this statement depends upon the following fact: When an investigation of the amount of work expended is made, as one gradually increases the work done—if, for example, one allows an individual to perform successively 100, 200, 300, 400, and 500 metre-kilogrammes of effective work per minute—one finds that the increased consumption of O_2 and of energy for every additional 100 metre-kilogrammes of work have each the same value. This result could not have followed if a restriction in the expenditure of energy during rest had occurred in any part of the organism with the object of supplying the energy entailed by the work done. If such a restriction occurred, this economy in the expenditure of energy would show itself to a marked degree in the case of the performance of a minimal amount of work; while, on increasing the amount of work done, the saving would not show itself to an equal extent, since the absolute amount of the restriction in expenditure must reach a limit at some point or another. Consequently, the first 100 metre-kilogrammes would require an apparently less consumption of oxygen than the later ones. This, however, is not the case, as has been shown by the foregoing details.[2]

The assumption, which has been confirmed by experiment, that the expenditure for work is added in its full amount to the metabolism during rest, forms one of the fundamental principles upon which is based the determination of "the useful effect of the work done within the organism" (*cf.* the following statements). Further, this fact has important bearings upon considerations of two kinds. In the first place, it is of importance for calculating what proportion of the total transformations of energy occurring during twenty-four hours can be utilized for bodily movement. This proportion consists only of the fraction of the daily exchange of energy remaining after deduction of the minimal exchange and of the expenditure for the work of digestion. The further consequence may be deduced that the heat formed in one organ (except in cases in which the external temperature is very low) cannot take the place of that formed in other parts. The life which is sustained in one cell by means of the oxidation associated with the development of heat cannot be maintained either by the heat formed by other cells or by that derived from without. A certain chemical exchange is necessary for the maintenance of the normal functions.[1] The formation of heat is a secondary, concomitant process, not the primary one. As a rule, heat loss is not a primary factor in the control of heat formation. On the contrary, the loss of heat adapts itself to the variations in the formation of heat associated with the functional activity of the organs.

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[1] An apparent exception to this statement is observed only in cases in which innervation of the muscles takes place with a view to heat regulation when the external temperature is low. This increase in metabolism, resulting from the heightened activity of muscles which are not performing effective work, naturally is suppressed if the heat requirements are covered by means of the work done.

[2] Possible exceptions occur when excessive work is performed, or when well-marked fatigue supervenes.

CONSUMPTION OF ENERGY BY DIFFERENT ANIMALS FOR THE SAME AMOUNT OF WORK DONE [FRENTZEL AND REACH (2)].

No.	*Type of Animal.*	*Working Weight.*	*Expenditure of Energy (Metre-kilogrammes) for—* Horizontal Movement Of 1 kg. over 1 m.	*Expenditure of Energy (Metre-kilogrammes) for—* Horizontal Movement Of ½ kg. over 1 m.	*Expenditure of Energy (Metre-kilogrammes) for—* 1 M.-kg. Work involved in Climbing.	*Distance in the Horizontal Movement per Minute.*	*Gradient of the Path in per Cent. of the Distance in the Case of the Climbing Experiment.*
		Kg.					Per Cent.
D. 1	Dog : miminal value	26·9	0·495	—	2·954	78·57	17·2
D. 2	Dog : maximal value	26·9	0·501	1·501	3·259		
H.	Horse : maximal value	456·8	0·137	1·058	2·912	78·57	10·3
1	Individual K. ..	55·5	0·223[2]	0·852[2]	2·857	74·48	9·6–13·3
2	" P. ..	72·9	0·217	0·907	3·190	71·32	6·5
3	" B. ..	67·9	0·211	0·861	3·140	71·46	
4	" N. Z. ..	80·0	0·288	1·241	3·563	51·23	30·7–62·0
5	" Sch. ..	88·2	0·263	1·171	3·555	42·34	
6	" A. L. ..	72·6	0·284	1·185	2·913	62·04	23·0–30·5
7	" L. S. ..	81·1	0·231	1·000	2·921	60·90	
8	" L. Z. ..	80·0	0·244	1·051	2·729	56·54	
9	Individual F. at normal rate of walking	86·5	0·219	0·974	2·746	66·94	
10	Individual F. at slow rate of walking ..	86·5	0·233	1·029		35·92	23·3
11	Individual R. at normal rate of walking	65·8	0·230	0·930	2·846	63·95	
12	Individual R. at slow rate of walking ..	65·8	0·251	1·014		34·58	

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[1] This metabolism admittedly varies according to the actual temperature of the cell.

[2] These two numbers are wrongly stated by Frentzel and Reach, as Zuntz has informed me. The above figures are the correct ones.

The foregoing summary by Frentzel and Reach (2) gives, in the first place, a review of the consumption of energy in metre-kilogrammes for the unit of work in the case of walking and climbing, calculated for a movement of 1 kilogramme of body-weight over 1 metre both in a horizontal and in a vertical direction.

The table shows that approximately the same expenditure of energy is required in the case of the different classes of animals—dog, horse, and man—for the work of pure ascent—*i.e.*, after deduction of the expenditure for movement in the horizontal direction.[1] An approximate expenditure of energy amounting to 3 metre-kilogrammes is required for each metre-kilogramme of the work performed in ascent. Consequently, 33 per cent. of the energy expended can be utilized as external work (2).[2] In round numbers the expenditure of energy in the case of the human subject may be stated as 3·0 metre-kilogrammes for each metre-kilogramme of the work involved in pure ascent (when the gradient is moderate). The expenditure for horizontal locomotion may be expressed as 0·2 metre-kilogramme for each metre covered and each kilogramme of body-weight moved. The "horizontal metre-kilogramme"—if we may be allowed to use this convenient expression, although it is not permissible in the strictly mechanical sense—requires, therefore, in the case of man,[3] approximately one-thirteenth of the expenditure necessary for one effective metre-kilogramme of work performed in pure ascent.

The work performed in descending was formerly assumed on theoretical grounds to be nil, or in other cases was stated to be equal to the work involved in climbing. Both views are erroneous. A limitation of expenditure, as contrasted with that involved in a purely horizontal movement, occurs when the gradient of the path is moderate and the surface good. When the surface is rough, as in mountainous regions, an increase occurs in the expenditure. This increase, however, is much less than that which occurs in an ascent. One finds, intermediate between these two conditions, a downward gradient, in the case of which the helpful, work-saving influence of gravity is just neutralized on account of the effort required for limiting the movements of the individual in his descent. This limit lies in the case of the horse at a gradient of 10 per cent. The saving is greatest when the gradient is 5 per cent., amounting to 40 to 45 per cent. of the expenditure required for horizontal movement. I base a calculation showing a saving of 14 per cent. in the case of the human subject upon two experiments of Katzenstein, carried out on a smooth surface having a downward inclination of 2½ per cent. Zuntz and Loewy found that the expenditure of energy required for movement over a distance of 1 metre on the track of a mountain railway having an incline of 25 per cent. was twice as much as that necessary for traversing the same distance over a horizontal surface. The purely vertical downward movement of 1 kilogramme over a space of 1 metre's length (" negative work involved in descent ") required in this case an expenditure of 1·20 metre-kilogrammes—*i.e.*, about 40 to 45 per cent. of the amount demanded for ascending the same distance (" positive work involved in ascent ") (4).

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[1] Since about 10 per cent. of the increased consumption of oxygen is claimed for the work done by the heart and by the respiratory muscles, the useful effect of the work may be stated still higher—namely, as 40 per cent. of the total, therefore higher than that yielded by the best artificial machines (20 to at most 33 per cent.). The theoretical effective value of the energy exerted by the muscles concerned in the actual raising of the body is, without doubt, still greater, since part of the muscles which are involved in climbing perform no external work, but serve merely as antagonists in the fixation of the skeleton, etc.

[2] We may leave out of account, as inaccurate, certain earlier measurements which differ from those above stated. The values obtained by Sondén and Tigerstedt, Johannson, and those of Kronecker's pupils agree to some extent with the results of Zuntz, if one takes into consideration the experimental conditions, which were partially unfavourable. I have recalculated from Gruber and Bürgi's papers the results of their final experiments on the work entailed in ascending (*i.e.*, those experiments performed after sufficient dexterity had been acquired), in accordance with the method of procedure adopted by Zuntz. That is to say, I have deducted the expenditure during rest and that required for horizontal movement from the total expenditure, and have inserted an average caloric value of 3·0 for each gramme of CO_2 (the O_2 had not been estimated). This calculation showed an expenditure of 3·0-3·6 metre-kilogrammes for 1 metre-kilogramme of work performed in ascent, and a useful effect of 27 to 33 per cent., therefore nearly the same values as Zuntz has found. The useful effect of 20 to 21 per cent. obtained by Atwater and Benedict in the case of an individual cycling on a suspended bicycle only holds good for the special experimental conditions adopted by them, in which for obvious reasons the useful effect must have a lower value. I can neither critically discuss nor here include the experiments of Chauveau, in the case of which an entirely different experimental method of procedure was adopted, and which are, in addition, affected by erroneous theoretical views.

[3] In the case of four-footed animals the expenditure of energy for the work involved in ascending is almost exactly as great as that in man. On the other hand, the expenditure for horizontal movement has quite a different value.

The expenditure of energy for 1 metre-kilogramme of actual work carried out in the rotation of the ergostat is somewhat greater than that expended in the work of ascending—namely, in the most favourable instance, after long practice = 4·0 to 4·3 metre-kilogrammes,[1] calculated from the best results of Heinemann (4). The useful effect amounting to 22 to 25 per cent. has, without doubt, so low a value partly on account of the fact that the human organism is little fitted for this type of work. A considerable number of muscles are thrown into action for the purpose of fixing the body. The result of their activity does not directly further the object of the work. This statement holds good in general for work done by the upper extremities as opposed to that done by the lower limbs.

Influence of Training.—All the numbers hitherto brought forward are only valid for ordinary work which does not produce fatigue, and for robust individuals who, without being trained in the athletic sense of the word, are yet fitted for this work and accustomed to it. When practice is wanting, the work is not performed effectively in the initial stages by otherwise capable individuals. Thus, one of the soldiers examined by Schumburg and Zuntz (5) when on the march over level ground, and while carrying a weight of 11 to 13 kilogrammes, showed on the first day an expenditure of 136 per cent.—the final expenditure being stated as equal to 100 per cent.—on the fourth day one of 123 per cent., on the seventh one of 122 per cent., and only reached on the thirteenth day his normal metabolism of 100 per cent., which was maintained later on at the same level. Examples of a similar decrease in the originally excessive expenditure of energy due to an increasing aptitude are to be found in the works of Kronecker's pupils, who were the first to study these conditions. If we state the quantity of CO_2 found in their experiments after training was complete, as 100 for each unit of work done, then a strong man, when in an untrained condition, expends 115 to 140 per cent. in climbing, and 135 per cent. in the case of work carried out on the treadwheel. The final low values that imply a sufficient training were only reached after fourteen days in the case of climbing [Gruber, Bürgi], while in the case of the obviously unpractical work carried out on the treadwheel they were only attained after fifty-five days [Schnyder; see also Johannson and Koraen (5)].

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[1] Similar values are given by Tigerstedt and Sondén. The expenditure is usually higher, as in the case of the individual examined by Katzenstein, who did not belong to the working-classes. The latter only showed a useful effect of 14 to 18 per cent., instead of the 23 to 25 per cent. attained by the worker examined by Heinemann.

Economy in expenditure is also reached in another direction in the case of athletic training. This saving in expenditure does not become manifest in ordinary exertions, in the carrying out of which the animal organism invariably works so effectively that the expenditure cannot be farther restricted, even by means of the most diligent practice, but only shows itself in the case of exertions involving a large expenditure of energy. While every increase beyond a certain limit in the work done per minute requires in the case of an untrained individual a marked additional expenditure for each extra unit of work done, this statement holds good to a much less extent in the case of the professionally trained athlete. The two professional pedestrians examined by Caspari required an expenditure of 0·426 and 0·428 metre-kilogrammes for each "horizontal metre-kilogramme" when travelling at a rate of 140 metres per minute—that is, an expenditure 11 per cent. less than that of the very expert amateur L. Zuntz (0·477 metre-kilogramme). Professionals are able to accomplish with great economy in expenditure even greater records, performances which are impossible for untrained individuals except during shorter periods of time. The vegetarian pedestrians just mentioned could traverse a distance of 172 to 183 metres per minute with an expenditure of only 0·490 metre-kilogramme. In this case the expenditure was only 15 per cent. higher than that required for the great speed of 140 metres (5).

Influence of Fatigue and Pain upon the Expenditure of Energy.

The expenditure of energy gradually increases even in the case of work which is not exhausting, and which can be carried out for hours at a stretch. Two army physicians examined by Schumburg and Zuntz consumed in the act of walking on the level after a march of 25 kilometres 5 to 18 per cent. and 2 to 9 per cent. more oxygen than in traversing the same distance prior to the march (6). L. Zuntz cycled at an average rate of 15 to 17 kilometres per hour for four successive hours. In this case the expenditure of energy increased, notwithstanding the absence of any feeling of fatigue, about 9, 13, 10, and 23 per cent. of the initial value after one, two, three, and four hours (6). Thus, if the same amount of work be performed for a series of hours, auxiliary muscles are gradually brought into action to a greater extent, partly for the performance of the work itself, partly for the fixation of the bodily framework. These muscles naturally carry out the necessary work with less economy in expenditure. The same reasons also afford an explanation of the increased expenditure occurring in the case of work which is from the first excessive and of too fatiguing a nature, whether it be too great in itself or unsuitably distributed over too small a proportion of the muscular system—*e.g.*, the severe labour entailed in turning a winch with one instead of two arms [A. Loewy (6)]. In the same way auxiliary muscles are called into play, and the O_2 expenditure is increased as soon as the onset of pain enforces a restriction in the action of the muscles at work. In one case the metabolism during a march was increased to the extent of about 20 per cent. in consequence of inflammation of the tendon sheaths of the foot [Schumburg and Zuntz (6)].

An increased consumption of oxygen is often observed at the beginning of moderate work in the case of men and animals who are in an absolutely fresh condition. It then, however, merely gives expression to the exuberant movements of the untired organism, which may well allow itself some prodigality in movement [Zuntz and Hagemann (6)].

A substantial increase of metabolism over and above that required for the performance of work has been noted in the case of the dog when it has become overheated, an event which is specially liable to occur when fatiguing marches are carried out in summer. It is the result of the rise in temperature which leads in itself to increased decomposition.

The temperature of the air does not influence the consumption of energy if its variations be within normal limits. The production of CO_2 remained the same for the same amount of work done when the temperature varied from 5 to 25° C. [Wolpert (7, *a*)]. Wolpert (7, *b*) assigns for the same amount of work performed in highly heated air a lower excretion of CO_2 than when it is carried out in air at a moderate temperature.[1] Variations in the atmospheric moisture do not produce any constant alterations in the production of CO_2 during work [Wolpert (7)].

Influence of Variations in the Rate of Walking on the Level, and Influence of Increased Gradients in Climbing, upon the Expenditure.

A rather steep gradient on hills or stairs having an inclination of 30 to 60 per cent. required, instead of an expenditure of 2·918 metre-kilogrammes, one of 3·559 metre-kilogrammes for the effective metre-kilogramme [Schumburg and Zuntz (8)]. In the same way the consumption increases with an increase in the rate of marching. Thus L. Zuntz required to expend 0·245 and 0·287 metre-kilogramme for the "horizontal metre-kilogramme" of work when travelling at speeds of 58 and 98·7 metres per minute respectively. That is to say, an additional consumption amounting to 0·41 per cent. of the original expenditure was required for an acceleration of 1 metre per minute, even in the case of these two types of walking, which are still within the normal limits (similar values are given by Schumburg and Zuntz). L. Zuntz had a work expenditure of 0·477 metre-kilogramme when travelling at the great speed of

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[1] AUTHOR'S NOTE.—This is doubtful. The CO_2 values are extremely variable, and one must bear in mind secondary effects.

140 metres per minute, or 8·4 kilometres per hour, employing, in the latter case, a running step but rarely made use of in actual life. The metabolism for the unit of work was twice as great as that required for a speed of 60 metres per minute. The expenditure in the unit of time at 2·4 times the speed amounted to 4·3 times that at the original velocity (8).

If the rate be slower than that maintained during a comfortable promenade (roughly 60 metres per minute), *e.g.*, the slow speed of 35 metres per minute or 2 kilometres per hour, the work done likewise requires an increased expenditure of about 7 per cent. as compared with that necessary for intermediate rates of walking, because a certain muscular effort is necessary for limiting the pendulum-like movements of the lower limbs [Frentzel and Reach (8)].

Influence of a Reduction of Atmospheric Pressure and of High Altitudes upon the Value of the Work done.

While a reduction of barometric pressure in the pneumatic cabinet from 760 to 450 millimetres produces an increase in the expenditure of energy [A. Loewy (9)], the expenditure of oxygen and energy for the unit of work done is increased at high altitudes—at least, in the case of lowlanders. Zuntz and Schumburg consumed when in the Bétemps Hut, at a height of 2,800 metres, 37 and 25 per cent. more oxygen for climbing than at sea-level; while at 3,800 metres there was a rise of 54 per cent. A. Loewy and L. Zuntz, who were in better training in consequence of the more protracted nature of their experiments, required only 10 to 20 per cent. more at the like altitudes. The consumption sinks when the individual has become accustomed to the altered conditions, but in any case does not reach its normal value even after fourteen days [Zuntz and Schumburg].

Bürgi, a Swiss, accustomed to mountain-climbing, found the expenditure of work at the beginning of his experiments to be about 10 to 15 per cent. greater at a height of 2,200 metres than at a height of 700 metres. After he had been climbing for ten to twelve days, the expenditure at the higher level was not greater than that at the lower. At a height of 3,000 metres it still showed an increase of about 10 per cent. One can readily understand that mountaineers and practised climbers, as long as unusual climatic conditions are excluded, perform the amount of work required for climbing as economically even at an altitude of 3,000 to 4,000 metres as under other similar conditions at sea-level (9).

The Energy Expenditure in Cycling.

The necessary data for the calculation of the energy used up in cycling have been furnished by the excellent work of Leo Zuntz (10). The values which he obtained in a series of investigations upon himself hold good for an active, experienced cyclist, but not for one who has undergone special training—as, for example, a professional rider. The bicycle was of the usual form and weight (15 kilogrammes), the track

INFLUENCE OF VARIATIONS OF SPEED AND OF GRADIENTS AS WELL AS OF TRAINING UPON THE EXPENDITURE OF ENERGY.

Type of Movement.	*Kilogrammes.*	*Expenditure of Energy in Metre-kilogrammes.*			*Horizontal Velocity per Minute.*	*Gradient.*	*Remarks.*
		For the Horizontal Movement of 1 Kg. over 1 M.		For 1 Kmg. Climbing Work.			
		Absolute Numbers.	Relative Numbers.				
Work involved in climbing on a moderate gradient up to 30 per cent. (1, 2, 3, 6, 7, 8, 9, 11)[1]	—	—	—	2·918	—	6·5–30·5°	
Ditto in the case of a steep gradient over 30 per cent. (5, 6)[1]	—	—	—	3·559	—	30·7–62°	
Normal walking (average out of 1, 2, 3, 6, 7, 8, 9, 11)[1]	—	0·232	—	—	56·5–74·5	—	
Normal walking (9+11)[1]	—	0·225	100	—	63·95–66·94	—	
Slow walking (10+12)[1]	—	0·242	107	—	34·6–35·9	—	
Ordinary walking	70	0·245	100	—	58	—	Leo Zuntz.
Rapid walking	70	0·287	117	—	98·7	—	
Quickest rate of walking	70	0·477	195	—	140·1	—	
Not athletically trained man (P) without practice	82·0	0·293	136	—	75·4	—	Reckoned according to table, P. 7, p. 252 of Schumburg and Zuntz's work; walking on the level with a load of 10 to 13 kilogrammes.
After three days	80·4	0·264	123	—	76·2	—	
After six days	82·7	0·263	122	—	76·3	—	
After thirteen days	82·4	0·216	100	—	77·5	—	

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[1] The figures inserted in brackets refer to the numbered experiments given in the table on p. 228.

a cement one, and the exercise was taken in the upright, not in the bent, position. Thus the numbers cannot, without correction, be employed in the consideration of cycling under other conditions. The energy expended per kilogramme per metre horizontal movement (70 kilogrammes weight of rider + 15 kilogrammes bicycle = 85 kilogrammes)—

At slow speed (9 kilometres per hour) = 0·239 metre-kilogramme.
At medium speed (15 kilometres per hour) = 0·245 ,, ,,
At fast speed (22 kilometres per hour) = 0·305 ,, ,,

Here also, as in the case of walking, the energy used up per work unit increases with the rate of movement. This depends upon, in the first place, the increase in geometrical progression in the resistance offered by the air.

For the same reason a strong head-wind raises the energy expenditure. Riding at a rate of 15 kilometres an hour against a head-wind of 10 metres per second, Zuntz found in one calculation that the energy expenditure amounted to 0·427 metre-kilogramme. Although in this case the air resistance is distinctly decreased by the bent position adopted by the rider, the work expenditure against such a wind is twice as great as in the absence of any such resistance. The expenditure in cycling is much less for the same distance than in walking, although the extra weight of the bicycle (15 kilogrammes has also to be moved.

The expenditure in the case of a pedestrian walking at the rate of 3·5 kilometres per hour is the same as that for a cyclist travelling at the rate of 6·9 kilometres per hour. *Cf.* the following table for equivalent expenditures at faster rates.

	Kilometres per Hour.						
(*a*) In the case of a pedestrian ..	3·5	4·0	4·5	5·0	5·5	6·0	8·4
(*b*) ,, ,, cyclist ..	6·9	8·0	9·2	10·6	11·9	13·6	24·0

That is to say, for the same expenditure of energy a cyclist riding at slow or medium speed covers twice, at fast speeds three times, the distance that a pedestrian does. As a matter of fact, a cyclist riding at medium speed can cover three times, on exertion four times, the distance that a pedestrian can in a given time without the same subjective sensations of fatigue. This is partly due to the stimulating subjective sensations of cycling, partly to an objective cause—viz., that in riding one has not the same slow periodic alternating movements of the legs that one has in walking. Zuntz could only indirectly arrive at the proportion of the total expenditure that was used up in the performance of the external work of the cyclist. Atwater and Benedict (10) have found that in the case of a most expert cyclist (I. C. W.) pedalling on a freely suspended machine, about 20 per cent. of the total energy expended was in the form of the frictional heat of the wheel. This percentage (the Nutzeffekt) is much smaller than in the case of the mountain-climber (33 per cent.); but as it is obtained under quite different conditions it cannot be transferred to the conditions under which actual cycling is carried out.

For the amount of work performed in swimming the useful work cannot be satisfactorily calculated, as the amount of mechanical work performed is so exceedingly small. The amount of air respired under these conditions is remarkable, amounting to 50 litres per minute even in quiet swimming [Kolmer (10)]. Although the amount of oxygen used up in this case has risen above that required by an individual at rest and on dry land, still, it is much less than the ventilation. In this case influences other than ordinary muscular work play a part—*e.g.*, low temperature, water pressure, etc. In the therapeutic employment of swimming, one must bear in mind the differences in the mechanical relations during respiration, etc., compared to those existing in other forms of exercise.

Energy Expenditure in Statical Work.

This has been frequently calculated in such cases as the carrying of weights on the back or in the arms, or by the arm when stretched straight out [Speck, Bornstein and Poher, Johannson and Koraen (11)]. In comparison with the extremely severe feeling of fatigue, especially in the case of the last-mentioned act, the increase in the amount of oxygen used up is extraordinarily small, because the sensation of extreme fatigue only permits of such exercise being carried out for a very short time. In the experiments of Bornstein and Poher the maximal increase only amounted to 70 to 80 per cent., while in " movement work " the increase was 300 to 1,000 per cent. (*cf.* table).

It is of practical interest to determine the energy expenditure in the case of men on the march bearing a load—*e.g.*, in the case of soldiers—since this is a subject of very great importance.

Zuntz and Schumburg have shown that in the case of military knapsacks up to a weight of 30 kilogrammes, and suitably fixed on the soldier's back, the work expenditure for a definite weight and distance unit did not rise. That is to say, if a soldier of 70 kilogrammes' weight without knapsack expended x litres of oxygen each kilometre, with a knapsack of 25 kilogrammes he would require $x\ (70+25)$ litres oxygen. Under favourable conditions, marching on a level road, the weight of the knapsack can be more economically carried than the same weight of the working body. This is due to factors concerned in the mechanics of walking.

Action of Massage on Energy Expenditure.

It is often asserted that, in virtue of the stimulating action of massage on the muscles and on the organism as a whole, the kneading of the muscles markedly increases metabolism. This is by no means the case. The increase in respiratory exchange during massage is very small. In energetic massage of the thigh or abdomen carried out properly the O_2 and CO_2 exchange only rose 10 to 15 per cent.—less, therefore, than in the case of slight finger movements—and the respiratory quotient was scarcely affected [Leber and Stueve (12)]. The increase in metabolism that is so frequently taken for granted as occurring during massage only occurs, if it should appear at all, indirectly by rendering the muscular and nervous systems more capable of performing work than they were previously.

(δ) *Cardiac and Respiratory Work during Muscular Activity.*

Part of the increased expenditure of oxygen in muscular activity is due to the increased action of the cardiac and respiratory musculature. Zuntz and Hagemann (15) calculated that, in the case of a horse at work, 4·3 per cent. of the increase was required for the work of the heart, 6 per cent. for that of the respiratory muscles. While in the animal 5 per cent. of the total oxygen intake of rest is required for the work of the heart during active muscular strain, in spite of the increase in the work of the heart, the amount of oxygen used up to supply the needs of that organ shows a relative fall to 3·7 per cent. or less of the total. The mechanical output of the heart—at least, during moderate work—does not rise in the same proportion as the increase in the general bodily work and the total oxidation. For example, should the latter rise to ten times the height of the normal, the work of the heart during the same time will only rise to five or six times the height attained during a period of rest, the reason being that during work the consumption of the oxygen of the blood by the general tissues is much more complete than during rest. In the resting horse 100 c.c. of arterial blood gave 5 to 6 volumes per cent. to the tissues, in the working animal 10 to 12 per cent. [Zuntz and Hagemann;[1] see also Chauveau (13)]. From the experiments of F. Kraus on human beings one cannot obtain values that can be made use of for the above purpose, owing to the necessarily limited character of the experiments.

In order to send ten times the amount of oxygen to the tissues, the heart requires to drive only five times the quantity of blood to them, because the consumption of circulating oxygen is twice as great as during rest. This multiplication of its work is accomplished by doubling its frequency, and doubling or trebling the volume of its output. The increase in the size of the heart that occurs during severe work is not always, therefore, simply the expression of a pathological dilatation, as it is frequently supposed to be, but, as Henschen rightly considers, a physiological necessity, in order that the active muscles may be supplied with a sufficiency of oxygen. The condition of the distended heart is only pathological when it is overdistended—that is to say, when it no longer recovers its normal resting volume after a period of recuperation. This recuperation period varies with the degree of strain. A similar variable period is to be observed in the return to the normal of the respiratory and pulse rate after every form of exercise.

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[1] From an average of all the experiments of Zuntz and Hagemann, the differences in the amounts of oxygen given off to the tissues during rest and work are smaller. I have simply selected the values which correspond to complete rest and severe muscular work. Johansson (13) calculates the mechanical work of his heart during rest as 723 metre-kilogrammes, that of the respiratory musculature 472 metre-kilogrammes per hour, the two together 1,195 metre-kilogrammes. If we regard the *Nutzeffekt* as amounting to 33 per cent., we can from the above numbers reckon for the activity of both systems an expenditure of 5 and 3·4 calories. Johansson's hourly exchange during absolute rest amounted to 66 calories (rest in bed, 81 calories). Of this sum, 8 per cent. (6) would arise from the heart's work, 5 per cent. (4) from the respiratory muscles.

Apart from an increase in the amount of the circulating blood, the work of the heart may be increased by a rise in the arterial pressure. It is still a matter of uncertainty whether during moderate work there is a rise in the mean pulse-pressure in man. This is certainly the case in the dog [Tangl and Zuntz], while in the horse the pressure falls [Zuntz and Hagemann (13)]. In the latter, however, the pressure rises during severe work; the work of propulsion on the part of the heart increases in geometrical progression as a result of the greatly increased velocity of the blood-flow. During very severe bodily work the increase in the work of the heart is, therefore, proportionately much greater than in moderate work, rising in this case, in spite of the increased O_2 output in the capillaries, at least in equal proportion with the total work, occasionally much higher. This is doubtless also true for man.

If, in the case of severe work, the total amount of blood circulating in unit time be calculated as about five times the normal, the amount circulating through the active muscles and their oxygen consumption must be increased to a much greater extent. Chauveau found in the case of the easily working levator labii of the horse seven times as much blood circulating during mastication as during rest. The velocity of the blood-stream through the rest of the body does not increase in like proportion, because even in severe exercise only a proportion of the muscles are actually contracting strongly (rarely more than one-half or two-thirds). The circulation in the resting muscles and in the other organs of the body increases but slightly or not at all. The same is true for the consumption of oxygen, which takes place to a much larger extent in the working muscles than one would be led to believe from an examination of the composition of the mixed blood from the right side of the heart, or that of the venous blood from the arm. The oxygen consumption of the active levator labii was, on an average, twenty-one times greater than during rest, while the maximal increase was thirty-five times as high [Chauveau (14)].

(ε) *The Increase in the Energy Exchange under the Ordinary Conditions of Daily Life.*

It is important to gain a general idea as to the extent of the rise in metabolism which is met with under such a variety of working conditions as may occur in ordinary daily life.

The following numbers are given in order to allow an easy and rapid calculation of the corresponding caloric and work equivalents to be made from the oxygen consumption:

For 1 c.c. O_2 an average caloric value of 4·85 calories, corresponding to a respiratory quotient of 0·850, has been taken. In the table there are given both the values of the mechanical work equivalent of the heat (in the physical sense), as well as the physiological work equivalent. The latter amounts to 33 per cent. of the mechanical work equivalent.

Oxygen Consumption.	*Heat Formation (Calories).*	*Work Equivalent.*		*Corresponding Amount of Fat.*
		Mechanical.	Physiological.	
C.c.	Cal.	Mkg.	Mkg.	Mg.
1·00	4·85	2·061	0·687	(0·51)
0·2062	1·00	0·425	0·142	(0·105)
0·485	2·353	1·000	0·333	(0·247)
1·455	7·06	3·000	1·000	(0·741)
CO_2 formation :				
1 gm. CO_2	2·90	1·233	0·411	With a R. Q. of 0·85
1 ,,	2·62	1·113	0·371	,, ,, 0·97
1 ,,	3·31	1·407	0·469	,, ,, 0·72

N. Zuntz has collected together in a very useful table the energy and food requirements of a man of 70 kilogrammes while performing different kinds of work. This table I reproduce with certain corrections which Zuntz has agreed upon. From a study of this table one can easily observe the increase in the metabolism per work as well as per time unit (the hour), in absolute as well as in percentage amounts (calculated from the rest consumption), also the amount of fat, the combustion of which would correspond to the energy required for the muscular work. With the exception of the exercises referred to under No. 3, 4*a*, 11, 13, and 8, all the others are average performances, such as might be carried out by a capable man for many hours during the day without any special strain. As may be seen from the last column in the table, which I have added to the original, the consumption during light work rises about 200 per cent., during moderate 300 to 400 per cent., and during severe work 600 to 700 per cent. and more, than during rest.

From some notes taken during walking tours I have calculated that the hourly increase for a strong pedestrian in good training (67 kilogrammes in weight), and carrying a load of 8 kilogrammes, amounts to 400 to 500 calories (*i.e.*, about six to seven times the normal minimum of about 65 calories). A speed of 6 to 7 kilometres per hour was kept up for three hours and longer without rest. During tours through hilly or mountainous country about 2,500 to 2,800 calories were used up during the day when walking was kept up for eight to ten hours.

The expenditure for the much more severe exercise of high mountain-climbing (about 4,000 metres), calculated from the height reached and the number of strides, amounted to 3,000 to 3,500 calories, undoubtedly much too low a figure.

The energy expended while climbing difficult rocks or precipitous cliffs covered with ice is extraordinarily great.

A soldier carrying a load of 20 to 25 kilogrammes for a distance of 27 kilometres during a march of from five to six hours requires 1,400 to 1,500 calories; the same individual with a load of 30 kilogrammes requires about 1,700 calories [Zuntz and Schumburg (16)].

ENERGY AND FOOD REQUIREMENTS OF A MAN (70 KILOGRAMMES WEIGHT WITH CLOTHING) FOR DIFFERENT KINDS OF MUSCULAR WORK, AND THE EFFECT OF THE VARIOUS FORMS OF EXERCISE ON THE SWEAT SECRETION [N. ZUNTZ (15)].

Muscular Work per Hour.	*Energy Expenditure per Unit of Work.*	*Increase of Metabolism during One Hour's Work.*		*Amount of Water, the Evaporation of which Corresponds to the Amount of Heat set free during the Work.*	*Percentage Increase in the Energy Exchange compared to the Minimal Standard (about 65 to 70 Calories).*	
		=Cal.	=Gms. Fat used up.			
(1) 3·6 kilometres over level road	40·3 per kilometre	144	16	249	215	
(2) 6·0 ,, ,, ,, ...	47·2 ,,	283	30	488	420	
(3) 8·4 ,, ,, ,, ...	78·6 ,,	660	70	1138	1,000	
(4*a*) 6·0 kilometres over level road, with 25 kilogramme load[1]	64·1 ,,	385	41	664	580	
(4*b*) 4·8 kilometres over level road with 25 kilogramme load[1]	59·3 ,,	285	30	488	420	
(5) Climbing 300 metres (30 per cent. gradient; easy climb)	49·0 per 100 metres	147	16	169	220	Without the amount used up for the horizontal movement carried out at same time.
(6) Climbing 300 metres, stiff climb (over 30 per cent.)	58·0 ,,	174	18	200	260	
(7) Ascent of stair—300 metres in a distance of 3,000 metres=10 per cent. rise[2]	89·0 ,,	267	28	376	400	
(8) 1,800 revolutions with ergostat (16·67 metre-kilogrammes per revolution)=30,000 metre-kilogrammes per hour[3]	0·216 per revolution	388	41	506	580	
(9) 9 kilometres cycle ride on level road ..	20·3 per kilometre	183	19	231	270	With average bicycle on a cement track. On an ordinary country road the consumption is greater.
(10) 15 ,, ,, ,, ,, ..	20·8 ,,	313	33	396	460	
(11) 22 ,, ,, ,, ,, ..	25·9 ,,	571	60	722	850	
(12) 9 ,, ,, with 3 per cent. ascent[4]	38·3 ,,	345	36	432	510	
(13) 15 ,, ,, on level road, with a head-wind of 10 metres per second	40·1 ,,	601	64	727	900	

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[1] No. (4*b*) was calculated by me as a normal standard under ordinary military requirements. (4*a*) [Zuntz] refers to conditions only rarely met with in the case of soldiers, although frequent with tourists and guides.

[2] The numbers in series (7) are calculated by Zuntz incorrectly, being too low; those given by me are minimal figures, probably not reaching the actual consumption.

[3] The best *Nutzeffekt* of 25 per cent. is not attained, but a lower one has intentionally been inserted; with the exception of (4*b*), (7), and (12), all the numbers are identical with those in Zuntz's table.

[4] The numbers in series (12) are calculated by N. Zuntz under the assumption that the surface of the rider's body exposed to the wind is diminished one-half by the bending of the body.

(ζ) *Maximal Functional Capability.*

This is stated in terms of the amount of useful work performed in one minute. Thus the work performed in raising the body in a series of climbing experiments by Zuntz's pupils, where the individuals were only moderately strong, amounted to 500 metre-kilogrammes per minute, while in two muscular men it reached 809 and 999 metre-kilogrammes [Zuntz and Schumburg (17)]. So also with the ergostat 500 metre-kilogrammes can be performed per minute in cases when the experiment only lasts for a short time, and this without excessive strain. When this rather unsatisfactory kind of work was persisted in for longer periods only 20,000 metre-kilogrammes were performed in the hour [Wolpert]. Speaking generally, one may say that an active man with a light load can raise his body (weight 75 kilogrammes) a height of 400 metres in the hour while climbing regularly and easily, and that an effective hourly work of 30,000 metre-kilogrammes in this form is nothing out of the common. A very strong man of 70 kilogrammes can easily perform one and a half times the amount of work above mentioned (600 metres ascent in the hour) for a period of one to two hours' hill-climbing, while, as I have often observed, the Alpine herdsman can without the least exhaustion perform double the amount (800 metres = 60,000 metre-kilogrammes per hour).

For short periods (minutes and seconds) much more work may be performed (the results of the different writers are reckoned for a body-weight of 70 to 75 kilogrammes):

Authors.	*Nature of the Work.*	*Duration of the Work.*	*Amount of Work (Effective Metre-kilogrammes) per Minute.*
—	Mountain-climbing, moderate work	Many hours	500
—	Mountain-climbing, heavy work	1 to 2 hours	750–1,000
Mosso (17) ..	Mountain-climbing, steep, 100 metres	3½ minutes	2,000
Blix (17) ..	"Treadmill" ergostat	30 seconds	2,400–3,600
Kraus (17) ..	Stair-climbing, with 10 kilometre load	15 ,,	3,700
Zuntz (17) ..	Stair-climbing, without load	30 ,,	4,300
Blix (17) ..	Stair-climbing, without load	4 ,,	5,700–6,000

The physical equivalent of the work done by an average workman was previously frequently given as 300,000 metre-kilogrammes per day. According to our present knowledge, three times the amount of energy, corresponding to a heat formation of about 2,100 calories, must be expended in order to carry out this amount of work. This is, however, very severe work, and for moderate work one may reckon about 1,400 calories. In individuals performing very heavy work, such as smiths, luggage-porters, etc., the amount of work carried out, as has often been determined from their diet requirements, amounts to 3,000 calories. In the case of American football players it was still higher, 7,885 calories being taken in their diet (insufficient ?) [Jaffa (18)]. By far the greatest, almost incredible, muscular performances are accomplished in sport. Two examples of the most extreme forms may be quoted. Atwater and Sherman made observations on the winner of the 2,000 miles bicycle race, in which, during the first five days, 539 kilometres were covered on an average in nineteen hours forty-one minutes (18). Calculated from Zuntz's data, the energy comsunption for this work amounted to not less than 11,300 calories, corresponding to a performance of 1,600,000 effective metre-kilogrammes work.[1] To this must be added the energy exchange in rest, corresponding to about 1,500 calories for a man of 61 kilogrammes. From the purely physical calculation by Sherman the amount of effective work is stated as amounting to 1,300,000 metre-kilogrammes—*i.e.*, about 20 per cent. less. This incredible amount of work was carried out for five and a half days consecutively, with a break of scarcely two to three hours for sleep. The distance covered in the first day was 30 per cent. greater than the average of the three days. Four or five of the other competitors were but slightly behind the winner in the amount of work performed.

The second example is that of the vegetarian winner in the last long-distance walk from Dresden to Berlin. This man walked, inclusive of rests, at a rate of 125 to 140 metres per minute (7·5 to 9·0 kilometres per hour), and covered the whole distance of 202 kilometres in twenty-six hours fifty-eight minutes. Caspari (18) has calculated, with extreme care, the O_2 consumption in this man walking at the above-mentioned rate, and from it he has reckoned that the energy expenditure for the whole march amounted to 12,280 calories, or in round numbers 11,000 calories in the twenty-four hours, without including the rest consumption of about 1,500 calories. These numbers are more likely to be too low than too high, as the fatigue and other similar causes which would raise the energy expenditure were not considered. Here it may be remarked that—in Germany, at least—in these competitive races the vegetarian is ahead of the meat eater. This is due, not only to the vegetable diet, but also to the enthusiasm for "the good cause" and abstinence from alcohol. In Germany, the non-vegetarian cannot compete with the vegetarian in the matter of endurance in these long-distance walks. The vegetarian is ahead in the matter of rapid pedestrian feats. The non-vegetarian has not the same ambition to excel in this most monotonous form of sport that his vegetarian brother has. The highly specialized training, so common among athletes in England and America, has not spread so widely among the people of Germany.

American athletes, as a rule, take large quantities of meat, and are at least the equals of vegetarians in the matter of athletic contests. Those who successfully completed the whole distance in the 2,000 miles race performed an even greater daily amount of work than the vegetarian in the long-distance walk, although in the former case the work was continued for five days consecutively. The condition of the five winners at the end of the race was astonishingly good, in spite of the immense labour.

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[1] As the amount of work in this case was less than in the cases referred to in Zuntz's table, owing to the training of the men, the light bicycles, etc., 15 per cent. has been deducted from Zuntz's figures. In addition, the wind resistance offered by the body has been reckoned as lower than in Zuntz's cases, as it has been taken for granted that, owing to the attitude of the riders, less surface of the body would be exposed to the wind (instead of Zuntz's 0·614 square metre, 0·307 square metre was taken). The influence of fatigue on the energy consumption has been disregarded, so that undoubtedly the numbers are rather too low than too high. According to Atwater, no pace-makers were employed in the rac

(η) *The Employment of Bodily Movement in Treatment.*

A consultation of the previous table will give the physician some idea of the amount of work which he can prescribe for his patients. The rules set by Oertel[1] (19), who was the first to accurately regulate the amount of work of his patients, can now be stated in terms of absolute work standards. In the case of invalids, especially at the beginning of treatment, only the lowest of the work standards (Nos. 1 and 9 in table) need be considered, and in calculating these it is essential to remember, not only that the absolute work standard of the patient is below that of the healthy person, but also that the small amount of work which they perform is accomplished with a far greater expenditure of energy than in the normal person. This is true especially of work with the ergostat, which is frequently prescribed by doctors owing to the ease with which its amount can be regulated. Fr. Kraus found that in healthy individuals 20 to 22 per cent. of the total energy expended in the rotation of the wheel was in the form of useful work, while in the case of persons suffering from anæmia, neurasthenia, or disease of the heart, the percentage was only 11 to 16 per cent.

Effective work of from 2,200 to 3,500 metre-kilogrammes per minute can be accomplished by healthy individuals in such an exercise as rapid stair-mounting when carrying a load of 10 kilogrammes. In the case of two anæmic patients it reached only 2,050, in some cardiac cases only 550 to 1,500, and in a patient suffering from Basedow's disease only 250 metre-kilogrammes [Kraus (19)]. (All these numbers are reckoned for a body-weight of 70 kilogrammes.)

In ordering any form of exercise, and in calculating its probable effect on the general condition, it is essential to carefully bear in mind the condition of the circulation, respiration, the degree of obesity, and any debility due to previous illness. Jaquet and Svenson (20) refer to an active, stout person who was able to perform the normal proportion of useful work (25 per cent.) when engaged in mounting stairs, while in the case of a less robust, stout individual the proportion was only 11 per cent. The performance of 580 metre-kilogrammes per minute did not specially strain the former, while 250 metre-kilogrammes in the same time markedly exhausted the latter. A robust but stout person is able to perform the same amount of work with the same amount of expenditure as a normal person [Brodien and Wolpert (20)].

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[1] He ordered his patients to walk on the first day 2 to 4 kilometres on the level road, on the second day only 2 kilometres, and on the third 5 to 6 kilometres. At a later period the exercise was taken on a road with moderate incline, and then gradually over a steeper one.

Schnyder gave an excellent example of the increase in expenditure of energy after severe illness and the slow return to the normal condition. The CO_2 excretion in the case of a convalescent patient after typhoid fever, when working on the "treadwheel," amounted to 240 per cent. in the second week of convalescence, and in the third to seventh week 174 to 209 per cent., during the seventh week with daily practice 135 per cent., and only after some weeks during which recuperation was taking place did it fall to the normal 100 per cent. (20).

This loss of power is very marked, and continues for a very long time after infectious diseases. A patient, convalescent from pneumonia, on the fifteenth day of his convalescence used up 1·5 c.c. O_2 for 1 metre-kilogramme of work performed in mounting stairs, while a typhoid convalescent used up 2·72 and 2 c.c. O_2 for the same amount of work (Svenson (20)].

L. Zuntz (20) gives some valuable hints as to the employment of cycling exercise for invalids. As the feeling of fatigue is much less in cycling for a given amount of work than it is in walking, there is much greater danger of overstrain in the case of the former than in other forms of exercise. This is true for the healthy person, and much more so for an individual suffering from cardiac or pulmonary disease. It is absolutely essential in such individuals to limit not only the speed, but the distance, and especially at the outset to most carefully avoid any cycling that entails climbing. A speed of 8 kilometres per hour, with an ascent of 3 per cent., such as Kisch thinks permissible, should only be allowed in the case of a stout individual when he is active and robust. It is rather trying even for the healthy person to keep up this slow speed on a steeply ascending road. On the other hand, in the case of corpulent individuals of lazy habit, cycling is a most valuable exercise, as they are compelled to perform more work than they would be inclined to do in walking.

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does not come into the question, as it does not break down during work (see section on Influence of Muscular Work upon Metabolism).

If it were the fats, or, as many believe, the sugar, then this should be shown from the respiratory quotient. The respiratory quotient must rise in the case of a meat or fat fed animal if the store of glycogen be drawn upon during work, while, on the other hand, it must sink on a predominating carbohydrate diet if the fat is much drawn upon during work. As a matter of fact, the respiratory quotient is only slightly altered in cases where the work is not of an exhausting nature, and at any rate it does not always take place in the same direction [Katzenstein, A. Loewy, Schumburg and Zuntz, Zuntz and Hagemann (3)]. This is equally true for omnivora, carnivora, and herbivora.[1] The respiratory quotient remains almost unaltered during work, whether it has been during the preceding resting period low on an almost purely fat diet, or high, as on a carbohydrate one. Thus, according to Heinemann (3), it amounted to:

	During Rest.	*During Work.*
On a fat diet	0·723	0·723
On a carbohydrate diet..	0·802	0·805

It is only after work lasting for some hours that the respiratory quotient sinks if the store of carbohydrate gradually falls about $\frac{4}{100}$ or $\frac{6}{100}$ [Schumburg and Zuntz (3A)]. It only rises when work of too exhausting a nature has to be performed, and the respiration and circulation prove insufficient to furnish oxygen for the overstrained muscles [A. Loewy (3)]. This, however, does not signify an alteration in the choice of the oxidized substances, but rather a cardiac or respiratory insufficiency.

It follows from the constancy of the respiratory quotient that, in whatever proportion the three types of food are utilized in the metabolism during rest, no sudden marked alteration in the ratio occurs when work is carried out. In the working condition, carbohydrates and fats participate as sources of the energy approximately in the proportion in which they exist in disposable form in the organism, and also to the same degree as they are called upon to furnish the needs of the resting organism.[2] (For the conditions existing in the starving or flesh-fed animal, see p. 239.)

In view of the fact that the store of glycogen in the body decreases during work, and can be completely used up, this appears not only striking, but scarcely correct. A preference on the part of the working musculature for sugar actually does exist, but it does not go so far that the carbohydrate dissolved in the fluids of the tissues and in the places of storage is exclusively, or even mainly, made use of. It only occurs when carbohydrates are present in excessive quantity in the diet. In this case, however, even the functional processes associated with the resting condition are mainly supplied by oxidation of the carbohydrates, and thus the respiratory quotient, prior to work being carried out, is high, and only shows a moderate rise during active work (*cf.* the numbers given on the next page).

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[1] Dog, horse, and man may be taken as examples.

[2] As the protein decomposition is not increased during work, it shows a relative decrease when compared with the N-free substances, the breaking down of which is actually increased during work.

Iso-Energy of the Three Food-stuffs during Work.

Even after all has been granted that has just been described, the question of the source of the muscle energy has not been entirely settled. Even if all three foods be used up in work, still their work values may be different. The question still remains open whether they defray the work expenditure with equal economy—that is to say, whether an equal proportion of their potential energy be transferred into useful work or not. Are there standards for the work expenditure (iso-energy) which are comparable with Rubner's isothermic values in the resting organism? The systematic investigations carried out in Zuntz's laboratory (4) have answered these questions in the affirmative. These investigations were carried out in the following way: The amount of work performed in ascending a track was accurately measured when the person was kept for a long period on a diet as far as possible limited to one type of the food-stuffs. At the same time, the amount of energy per work unit was calculated as calories (or metre-kilogrammes) in the way already described. It was found that a dog, when performing work, transformed an equal proportion of potential energy for each work unit, whether it were fed principally on protein or fats or carbohydrates [Zuntz and W. Loeb].

As it is impossible to keep a man on a purely protein diet, only the fats and carbohydrates could be compared as sources of energy. In Heinemann's experiments, work was more economically performed on fats than on carbohydrates. His experiments, however, were vitiated by certain fallacies and irregularities. Frenzel and Reach employed work that entailed climbing as their standard, instead of that employed by their predecessors—namely, rotating work with the ergostat, a method which is much less suitable for exact experiments. The net effect on a fat and on a carbohydrate diet was practically equal (4). It amounted to:

	The R. Q.[1] in Rest.		*The R. Q. during Work.*		*Work Expenditure per Work Unit in Calories.*	
	F.	R.	F.	R.	F.	R.
On a fat diet.. ..	0·759	(0·752)	0·773	(0·781)	2·066	(2·119)
On a carbohydrate diet	0·876	(0·937)	0·889	(0·900)	1·980	(2·086)

The experiments of Atwater and Benedict (4) were carried out in a somewhat different way. The increase in the energy expenditure was not estimated during the period when work was actually being done, but for the twenty-four hours. A moderately large amount of work was carried out in the form of cycling. The principal person—J. C. W.—riding for eight hours, performed actual work to the value of 534 calories, and for this 2,677 calories were expended.[2] On a mixed diet, sufficient to cover requirements, a part of the energy (1,800 calories) was introduced alternately in the form of fats and carbohydrates, while the rest of the diet remained unaltered.[1]

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[1] The respiratory quotient rose on an average of all experiments with both individuals from 0·756 to 0·777 on a fat diet, and sank from 0·907 to 0·895 on a carbohydrate one (see also p. 235).

[2] The work performed on the suspended wheel was transmitted, etc., to an electromotor, and measured directly as heat.

Each series consisted of eight or six working days, half being "fat," half "carbohydrate" days. Collectively, there were four such series from which calculations could be made, these covering a period of thirty days—fifteen on a carbohydrate and fifteen on a fat diet. The results showed that, as energy dispensers, the fats were somewhat behind the carbohydrates, the former furnishing only 95·5 per cent. (92·8 to 98·3 per cent.) of the amount which isodynamic portions of the latter provided.

In two other persons doing less work, an exclusive fatty diet was found to be somewhat more economical. Atwater and Benedict ascribed the smaller yield of work in the case of J. C. W. on a fat diet to a special idiosyncrasy on his part, and therefore do not look upon this effect as constant nor as essentially due to the organization of the working machine. (For the action of fat and carbohydrate diet in the protein metabolism during work, see the next section.)

These experiments absolutely confirm the theoretical conclusions drawn from Zuntz's experiments. Owing to their short duration Zuntz's experiments sufficed merely to set forth a scientific law that carbohydrates and fats are in principle equal in value as sources of muscle energy. From the nature of the American experiments, it has been shown definitely that, for the practical conditions of daily life, fats and carbohydrates may be exchanged for one another in a mixed diet, and still maintain the amount of energy disposable for work at the same level.

Does the Working Muscle make use of the Fat and Protein after their Transformation into Sugar?

Although the above experiments prove the equality of the fats and carbohydrates as dispensers of energy, they give no definite evidence as to the nature of the chemical process by which these bodies are made use of. It is, for example, conceivable that the contracting muscle always makes use of one body only—namely, glucose. If this were so these fats and proteins would require to be transformed into glucose before they could furnish the necessary energy for muscular work, a view actually held by many investigators.

In spite of the evidence brought forward by Seegen, and also of experiments on the diabetic organism, no definite proof has been given of the formation of sugar from the higher fatty acids in the tissues. Still, the possibility of this mode of formation in some physiological and pathological conditions cannot be denied, and it must be borne in mind in any discussion bearing on the use of fats during work. If this supposition should prove to be correct, there is—at any rate, in the transformation—no loss of energy. Such a loss of energy is, however, unavoidable if the hypothesis of Chauveau and Seegen as to the nature of this transformation be correct. According to Chauveau, the transformation of fat into sugar takes place outside the muscles. But the amount of sugar which can, according to Chauveau, arise from fat is only 71 per cent. of the potential energy of the fat,[1] or 74·6 per cent., if one accept the quantitative transformation of the carbon of the fat into the carbon of the glucose.

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[1] In all the experiments, therefore, in addition to a fixed quantity of protein, varying amounts of fat and carbohydrate were consumed, neither of these last two bodies ever being completely absent from the diet. A clear difference exists between these and Zuntz's experiments, where every care was taken to exclude as completely as possible one of these bodies from the diet. The total energy requirements of J. C. W. (the American) amounted on an average to 5,000 calories, of which 2,677 calories were spent on work (excess of "work" days over "rest" days). The food intake amounted to 4,000 to 5,000 calories, so that 5 to 20 per cent. of the requirements must have been furnished by the body fat.

100 grammes glucose = 40 grammes C = 369·2 calories.
100 grammes fat = 76·5 grammes C = 946·1 calories.
1 gramme glucose-C = 369·2 : 40 = 9·23 calories.
1 gramme fat-C = 946·1 : 76·5 = 12·37 calories.

$$\frac{\text{Glucose-C}}{\text{Fat-C}} = \frac{9{\cdot}23}{12{\cdot}37} = 74{\cdot}6 \text{ per cent.}$$

Twenty-five to twenty-nine per cent. of the energy of the fat is therefore lost in the transformation occurring outside the muscles, and only 71 to 75 per cent. is at the disposal of the working muscles. That the fats, however, are less used than the carbohydrates as sources of muscle energy to this extent has been definitely shown to be incorrect by the experiments of Zuntz and Atwater. In order to prove this transformation of fats into carbohydrates one has to accept certain hypotheses whose admissibility is doubtful; at least, it must take place within the muscles and without loss of energy for the work requirements (5).

The possibility of a splitting off of sugar from protein in muscular activity is one which lends itself much more readily to discussion. Certainly it can only occur when the organism is exclusively, or, at least, amply supplied with proteid nourishment. In this case also, as the experiments of Zuntz and Loeb have shown, there can be no loss of energy in the transformation. Certain facts can, however, be adduced in favour of the possibility of the occurrence of such a process in the case of, or, better, for the purpose of, the performance of work. In cases where there is a deficiency of carbohydrate, as in hunger, or on a purely flesh diet, sugar is obtained by protein decomposition, and is stored as glycogen. This process occurs during rest, and hence the respiratory quotient of a man in starvation and not performing work is relatively too low; and the same holds for the dog on a flesh diet[2] [Zuntz and C. Lehmann, Frentzel and Schreuer (6)] (see section on the Respiratory Quotient). Under these conditions, when work is performed, the respiratory quotient rises distinctly, in the experiments of Zuntz and Lehmann from 0·700 to 0·797, and in those of Frentzel and Schreuer from 0·73 to 0·79. The conclusion, that in this case the glycogen that had been previously stored is now burnt up, is undoubtedly correct. Here the periods of the formation of sugar from protein and the combustion of the former are separated from one another, and so the proof of the transformation is rendered possible.

One may not, however, conclude from this that the protein under normal conditions can only furnish the energy for mechanical work by such a transformation. In fact, the probabilities are against such a supposition being correct.

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[1] The sugar is already more highly oxidized than the fat.

[2] It often is below the theoretical limit of 0·72.

Alcohol and Muscular Work.

It is quite as difficult to decide whether alcohol may serve as a direct source of energy for muscular work. One can scarcely believe that such is the case. Indirectly, however, it may act in this way, just as in rest, by replacing equivalent quantities of fat and carbohydrate as a source of heat, and thus allowing these two food-stuffs to be at the disposal of the contracting muscles. In this way alcohol may serve indirectly as a source of energy for muscular work, but only by taking the place of fats and carbohydrates as a heat-producer, and leaving these free for the first-mentioned purpose. It certainly acts in this way when taken in moderate quantity. When 72 grammes of alcohol were taken in the course of the day in place of an isocaloric amount of fat, the total metabolism on the alcohol days was no greater than on the alcohol-free diet, in both cases the same amount of work having been performed [Atwater and Benedict in numerous series of experiments of some weeks' duration[1] (7)].

Alcohol, therefore, in this quantity does not lower the energy value of the other food-stuffs—at least, not directly and immediately.

As can be readily understood from daily experience, when larger intoxicating quantities are taken the work is performed most uneconomically, and a much smaller amount can be satisfactorily carried out than under normal conditions [F. Kraus, Chauveau (7)].

Practical Experiments on Dietetics with a View to the raising of the Functional Capacity.

During recent years sugar has been recommended as a suitable food-stuff for raising the capacity for work of a prolonged and severe character, and so cane-sugar has been added to the soldier's rations. Here, however, other problems than the purely nutritive one had to be considered, especially political ones dealing with the land question and the sugar industry. It appears quite a rational procedure when one remembers the distinct preference shown by the contracting muscle for sugar and the rapid absorption of sugar into the circulating fluids. From a large series of experiments with Mosso's ergograph it has been shown that the consumption of sugar revives the muscles of the forearm when they have become fatigued. Frenzel (8) has, however, correctly shown that this invigorating action can scarcely be explained so easily. The work done with Mosso's ergograph exhausts, it is true, the glycogen present in the contracting muscles, but these only constitute a small and limited group, while the large glycogen stores in the rest of the body are unaffected, and are still at the disposal of the exhausted muscles.

Frenzel carried out a series of well-planned experiments with the large ergograph, and he confirmed the invigorating action of sugar in exhaustion, but he found that protein in isodynamic quantities was much more effective.[1] For the first two hours after consumption the effect was the same as with sugar, but while, in the case of the saccharose, the effect had worn off by the end of the third hour, in the case of protein the invigorating influence remained until the seventh hour.

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[1] The experiments were of similar nature and duration to those described by the same authors in which fats and carbohydrates were compared.

This increase in muscular power which sets in so rapidly certainly depends on several causes. In the first place, there is the influence of reflexes from the stomach and intestine, also the direct action of the absorbed food-stuffs on the muscles themselves, and, above all, so it appears to us, an action on the nervous system. For the accurate analysis of the nature of these actions much more investigation is required.

There is a certain amount of interest in the question as to the therapeutic value of this invigorating property of protein.

V. Noorden, following the English method, has obtained very good results from giving a full meat diet (at breakfast and lunch) to young women suffering from chlorosis and also in neurasthenic cases—that is to say, in individuals whose will-power and muscular strength are low during the first half of the day. It is quite probable that the desire for protein, often expressed by those in training, depends, in part at least, upon these physiological effects.

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(c) Influence of the Different Systems of the Body on the Energy Exchange.

NERVOUS SYSTEM, GLANDS, CONNECTIVE TISSUES, THYROID, REPRODUCTIVE ORGANS.

1. *The Nervous System and Metabolism.*

"Mental work exercises no direct influence on metabolism. The molecular changes which are characteristic of and which lie at the foundation of all mental processes are neither oxidation nor decomposition processes, or, if they are, they are too slight in degree to be calculable by our present methods" [Speck (1)]. There was neither any alteration in gaseous exchange nor in heat formation when intense mental work was engaged in, either for a short period [Speck] or for longer periods [three days—Atwater], the standard for comparison being the metabolism of an individual in a condition of complete mental relaxation. The same holds true for the metabolism of protein [Oppenheim], and probably also for that of the inorganic salts. In the case of the person examined by Atwater the excretion, in periods of three days, was as follows :

	Output.		*Absorbed from Food.*	
	Heat.	*N.*	*Calories.*	*N.*
Severe mental work	2,620 calories	13·1	2,520	14·8
Mental rest	2,695 calories	12·5	2,495	14·8

For shorter periods, as Oppenheim and Speck have shown (3), the N and urea excretion are unaffected by mental processes. In the case of the older experiments, where reference is often made to an increased N and P_2O_5 excretion during mental work, there must have been some error introduced into the method of investigation. The statements that an increased P_2O_5 excretion arises from a using up of nervous matter rich in phosphorus rest upon preformed opinions or fallacious interpretations (see Speck's criticism).

Sleep and darkness do not diminish metabolism in man; thus mental activity does not increase it. Although this is true, there is no doubt, as the clinician holds, that the nervous system exercises a profound influence upon the general bodily condition. Mental work and subjective sensations of a pleasant character increase general exchanges, and promote the sensations associated with the healthy organism, just as light, sun, and air do. But the stimulation of metabolism which all these produces is always an indirect one, due to a conscious or unconscious increase in muscular activity brought about through the nervous mechanism.

2. *The Influence of Glandular Work upon Energy Exchange.*

The glandular organs, which in the matter of protoplasmic content are placed next to the muscles, must, when active, be the seat of great metabolic activity, and as a result must set free a large amount of heat. One would naturally expect this to be the case. The best proof of the correctness of this view is to be obtained from C. Ludwig's (4) discovery of the rise in temperature (1 to 1½°) of the venous blood coming from the submaxillary gland after chorda tympani stimulation (1). An accurate measurement of the heat output of all glands is impossible, but undoubtedly it must be very great. The daily quantity of the digestive fluids in man amounts to much more than 5 litres. The collective activity of the digestive glands most certainly raises metabolism, but it must be remembered that the work of the smooth muscles of the intestines and the energy required for the working up of foodstuffs in other organs also play parts in the work of digestion, so that it is impossible to gauge the amount expended in pure glandular activity.

The metabolism of the largest gland in the body, the liver, must be very great, but it does not lend itself to calculation, as only a part of the heat formed is given off in the external secretion.

Increased secretion of water by the kidneys does not increase the CO_2 excretion (for particulars, see section on Water). Although, as Dreser has shown[1] (5), the osmotic work of the kidney is so great, still, when merged in the total work of the organism, it appears but an insignificant part.

3. *Connective Tissues.*

These have only a very slight metabolism, and any variations produce no effect upon the total exchange. For the significance of fat deposits, see section on Fat.

4. *Other Systems.*

The share taken by the blood-forming apparatus and the ductless glands in the general metabolism is unknown. The thyroid and, according to some, the reproductive organs have a marked influence upon the general metabolism. This is discussed, however, in separate chapters (*cf.* the section on Influence of the Reproductive System on Metabolism, and the chapter on the Ductless Glands in the pathological part of this book).

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[1] H. Dreser calculates the work done by the kidneys in excreting 1 litre [from the osmotic pressures of the blood ($\Delta = -0{\cdot}56$) and urine (average $= -2{\cdot}3°$)] as 185 metre-kilogrammes—*i.e.*, for the daily quantity of 1½ litres 280 metre-kilogrammes, or, in terms of heat-value, only ⅔ calorie. The work of the kidney does not consist merely in the concentration of the urine.

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5. Influence of External Conditions on the Fundamental Metabolism.

(1) CLIMATE (LIGHT, SUN, WIND, MOISTURE, HEAT AND COLD, HEAT REGULATION, SEASONS, AND ZONES).

(*a*) *Influence of Light and Sunshine.*

The beneficial action of light on the body and the mind has been long recognised. It was explained by the older school as the result of the stimulating action of light upon chemical processes directly increasing metabolism. Numerous animal experiments have shown clearly that there is an increase in the gaseous interchange, but this increased metabolism is exclusively brought about by active muscular movements, for if these be absent—as, for example, in caterpillars [J. Loeb], or in curarized frogs—or if they are voluntarily inhibited in man, then light does not produce this effect.

Speck, in a series of experiments upon himself, arrived at the following results :

Per Minute.	*Ventilation.*	*O_2.*	*In CO_2.*	*R. Q.*
	C.c.	C.c.	C.c.	
With open eyes	6,446	277	233	0·842
With firmly-closed eyes ..	6,017	273	223	0·817
Difference	+7 per cent.	+1½ per cent.	+4 per cent.	—

The activity of the stimulated nerves *per se* causes no increase in oxidation—at least, not to such a measurable extent as to influence the general metabolism [Speck].

Sunlight has also had ascribed to it a very marked influence upon general metabolism. Rubner and Cramer (2) found in their experiments on dogs that it was merely the expression and result of the heat rays upon the body. This is not the case in man, where the regulation at higher temperatures is different from the dog [Wolpert (2)]. In still air, at a temperature of 20° C. and with clothing, or from 25° to 30° and without clothing, bright sunshine has no more influence on the O_2 and CO_2 exchange in man than darkness under the same conditions of temperature and clothing [Wolpert].

Although this is uncertain, there can be no doubt about the favourable influence of light and sunshine in healthy persons and in invalids, both exercising a beneficial and stimulating action upon metabolism. They do not accomplish this in virtue of any immediate action upon the oxidation processes in the resting cell, but indirectly in so far as they increase active movements. It is the mental action exciting greater bodily activity by raising the potential energy of the nervous system. There is no direct transformation of this energy into movements; the nerve energy acts by setting free the muscular. And since psychical influences are more marked in man than in the lower animals, these undoubtedly play a more important part in the former than in the latter. As light and sunshine frequently give rise to muscular activity, so the bodily metabolism may be increased, the appetite and absorption improved, the action of heart and lungs strengthened, and the circulation of the tissue fluids favoured, etc. In this sense, therefore, light and sunshine may be regarded as exceedingly important therapeutic remedies.

The skin, which becomes pigmented and shows better circulation as a result of the sun's action, sends a large number of afferent impulses to the brain, and these increase reflexly the activity of all tissues, and render the organs more capable of performing their normal functions. A scientific explanation of the remedial action of light, sun-baths, etc., cannot at present be given owing to the impossibility of accurately gauging the influence of the different factors—cooling, effect of winds, etc.

As has been previously emphasized, a direct influence of light upon oxidation processes in the tissues has not been scientifically proved.

(β) *Other Atmospheric Influences.*

There are also other atmospheric conditions which *per se* have no immediate influence on metabolism. A strong wind raises the CO_2 excretion, but only when the temperature is low, and, therefore, merely in virtue of its cooling effect [Wolpert (3)]. (The increase is almost certainly due to active movements being carried out to counteract the cooling effects.) It has no such action if the temperature is high. Alterations in the tension of the water vapour affect neither the CO_2 excretion nor the metabolism of nitrogen and fat [Rubner (for the dog), Rubner and Lewaschew (for man); this is true also for rest and sleep as well as for work, Wolpert (3)].

(γ) *Action of Cold and Heat.*

A fall in the external temperature increases the heat formation, the CO_2 excretion, and the oxygen consumption in warm-blooded animals. If the external temperature rise very gradually, a normal condition is reached with the lowest metabolism at moderate temperatures, while at higher temperatures the metabolism is somewhat greater. Here it may be taken for granted that the body temperature of the animal does not appreciably fall when subjected to the influence of the cold air. It is quite otherwise with the cold-blooded animal, whose oxidation processes sink with the temperature of the surroundings. With a rise in temperature of the air the increase in metabolism in warm-blooded animals is less than when the temperature falls, the body temperature rising slightly. The increase is much greater if the animal be placed in hot or cold water than if it be merely subjected to the influence of cold or hot air (4).

The alterations in metabolism in cold and warm air are less marked in man than in the small animals employed in laboratory work. This is due partly to the greater body mass of the former, and also to the protective action of the clothing. When the external temperature is high, man is also much better equipped for regulation of body temperature than are dogs and rabbits, which do not perspire. Still, in experiments on man the same influences of heat and cold are to be observed as in the case of the other warm-blooded animals [C. Voit, Rubner (5)].

CO_2 Excretion in Man (Grammes per Hour) at Different Temperatures (Centigrade).

		4°.	6·5°.	9°.		14·3°.	16·2°.			23·7°.	24·2°.	26·7°.		30°.	
Volt	—	35·1	34·3	32·0	—	25·8	26·4	—	—	27·5	27·7	26·7	—	28·4	—
						26·1				27·3					
	2°.				10–15°.	15°.		15–20°.	20°.	20–25°.		25°.	25–30°.	30–35°.	35–40°.
Rubner. 1.	—	—	—	—	39·9	—		28·1	—	30·5		—	—	—	—
Rubner. 2*a*.[1]	—	—	—	—	—	32·3		—	30·0	27·9		31·7	32·4	—	—
Rubner. 2*b*.[2]	—	—	—	—	—	34·0		—	28·3	28·6		31·4	—	—	—
Rubner. 3.	29·8	—	—	—	25·1	—		24·1	—	25·0		—	25·3	23·7	21·2

[1] Dry air. [2] Moist air.

The variations in the CO_2 excretion at different atmospheric temperatures do not rise above 30 per cent. The influence of hot and cold water is much more pronounced. In the case of cold baths or douches the O_2 and CO_2 exchange may increase 50, 100, or 200 per cent. [Liebermeister, Loewy, Rubner; in hot baths an increase up to 50 per cent., and even 100 per cent. has been noticed [Winternitz, Rubner (6)].

Heat Regulation.

General Remarks.—The significance of an increase in heat production in cold weather is clearly the maintenance of the normal body temperature under conditions when there is an increased loss of heat. In Nature this regulation plays a most important part, and full advantage is taken of it in the practice of medicine. How is this regulation brought about? Formerly it was taken for granted that cold *per se* stimulated the cells of the resting organism to increased activity. Senator (7) was the first to call this in question. He explained the increased CO_2 excretion as being due to active movements, and held that in the absence of the latter the former showed no alteration. Speck held practically the same opinion. A. Loewy and Johansson's experiments (see later) (7) settled decisively the question. At present no one doubts that, when there is an increase of 100 per cent., or more, as after cold baths, this must be due to active movements.

These are either voluntarily produced, or reflexly in the form of shivering tremors. The only question that is still open for discussion is whether there may not be a slight rise in the CO_2 excretion without any visible movement or alteration in the tension of the muscles. An increase up to 20 to 30 per cent. has often been observed under the influence of cold in individuals apparently at absolute rest (see table on p. 245).

The question whether there is an involuntary heat regulation has been answered in the affirmative by the earlier workers as well as Voit (from animal experiments), and also Rubner.

One can only judge as to the resting condition in animals from observation. But this is a matter of great difficulty, as it is only our subjective sensations that give us the necessary information, and so it is only the experiments on man that can furnish the decisive answer. A. Loewy has shown from his investigations on doctors and other educated persons, and Johansson from observations made upon himself, that the gaseous interchange remains absolutely unaffected by cold, if all movements, whether voluntary or reflex (shivering), and also every tendency to an increased muscular tonicity, be carefully avoided. As, however, it is only the muscular activity and not the chemical decomposition processes in the resting individual which are under the influence of the will, we are led to conclude that a rise in the heat formation under the influence of cold cannot take place in the human being in the absence of movements of all kinds. As Rubner has correctly emphasized, the suppression of shivering and the inhibition of every movement is an unnatural condition for a person subjected to great cold, and one that never occurs normally. It is, however, the essential nature of all experimental work, concerned in the recognition and analysis of the different causes that may produce a certain effect, to create abnormal and artificial conditions, so as to enable one to recognise the nature of each separate influence that may be concerned (7).

(δ) *Regulation of Body Temperature by Variations in Heat Production and Heat Loss—Chemical and Physical Heat Regulations.*

As a supplement to what has just been described, some remarks on the regulation of temperature are here collected together.

Heat regulation may be necessary—

1. To avoid overheating:
    - (*a*) In cases where there is diminution in heat loss (high temperature of surrounding air).
    - (*b*) Where there is increased heat formation (muscular work, etc.).
2. To avoid cooling:
    - (*a*) In cases of diminished heat production (rare, usually pathological).
    - (*b*) In cases of increased heat loss from fall in outside temperature.

The following are the means of regulation:

1. A regulation by means of alteration in heat dissipation (Rubner's physical heat regulation).

2. A regulation by means of altered heat formation (Rubner's chemical heat regulation).

These may supplement one another. Increased production and diminished loss have the same influence on the body temperature, and the same holds good for diminished formation and increased loss.

(1) *Alterations in Heat Loss* (*Physical Heat Regulation*).

An increase in heat dissipation by means of conduction, radiation, and evaporation comes into play as a means of avoiding overheating [1 (*a*) and (*b*)], a diminution, on the other hand, preventing lowering of the body temperature [2 (*a*) and (*b*)]. In the section on the part played by water in the animal economy, a description is given of the mechanism and the degree of physical heat regulation, so far as it is dependent upon alterations in the excretion of water. While an increase in the loss of water can take place to an almost unlimited extent, except in the case of certain abnormal conditions of the surrounding medium, a diminution in the water excretion is confined within much narrower limits. The restriction of the heat loss is not sufficient to maintain the normal body temperature in all cases when conditions are present which lead to a marked cooling down of the surrounding medium [Speck, Loewy, Johansson (7)]. The amount of heat present in the body falls under the influence of cold, and it does not rise, even when the individual is placed in a warm bed, until active movements again furnish the necessary amount of heat to raise the temperature to the normal [Johansson].

(2) *Alterations in Heat Production* (*Chemical Heat Regulation*).

In the chemical, just as in the physical heat regulation, there is a limit below which it cannot take place. The chemical energy set free in vital processes which is inseparably associated with the development of heat cannot go below a certain limit. Only that form of heat production previously referred to as associated with the increase in functional capacity of working organs can be excluded. At least, in the starving organism only the disappearance of the muscular activity comes into question, as the " metabolism of the digestive process in the wider sense has already reached its minimum."

If, as in Rubner's Series III., p. 245, an individual excreted, at a temperature of 35° to 40° C., 2 to 4 grammes CO_2 less in the hour than at medium temperatures, this, in our opinion, was due to the fact that at 25° C. there are slight muscle movements which are either absent at a temperature of 40° C., or are very much diminished. A restriction of the " fundamental or minimal metabolism " cannot take place, as many experiments on animals and men have shown, although it is impossible for us to analyze each case. Previously, on the evidence brought forward by the curari experiments of Röhrig, Zuntz, and Pflüger (8), it was believed that a decrease of muscular tonus produced a diminution in heat formation in the muscles, and as a result a fall in the total energy exchange. So long as these experiments were regarded as correct it was generally held that at higher temperatures a relaxation of muscles could take place through diminution in the tone of the muscles. At a later period Frank and Fr. Voit (8) showed that curari produced no diminution in metabolism in an animal kept absolutely at rest, and so the older view has been abandoned.

At medium atmospheric temperatures there is a definite diminution of metabolism, a sure proof that the chemical processes in this case are independent of the exigency of heat production. They are essentially requisite for the maintenance of life and the normal bodily functions, the heat formation appearing only as a secondary effect.

There is no upper limit for chemical regulation. Active muscular work can raise the amount of combustion to such a height that even in cases of the greatest withdrawal of heat from the body the maintenance of the normal body temperature can be maintained for a certain time at least. This regulation can only take place by means of muscular movements. Without these there is no chemical regulation in man. And it is just around this question that the discussion of many years has turned. Rubner (8A) has recently defined chemical regulation as concerned with these vital processes, by which the maintenance of the body temperature is preserved—that is, by an increase of heat production in the resting animal. He merely interprets the term "rest" in a different way. At present greater unanimity of opinion exists on this subject [see also Johansson (7, *b*)].

While oxidation is increased when the external temperature rises, apparently only, however, when accompanied by an increase in the body heat, cold, on the other hand, according to our view, has no immediate influence on the metabolism of the resting cell.

(ε) *Influence of the Zones and Seasons on Metabolism—Influence of Acclimatization and Race.*

In the previous paragraphs, practically all the information has been given which would be required to decide questions relating to the "heat balance" in warm and cold climates in summer and winter. The older doctrines, based upon incorrect conceptions, which referred to a diminution in metabolism in the tropics and during the hot months in our own country, have been shown to be incorrect.

In the first place, the great differences in temperature which occur in different zones do not produce their full effect either upon men or animals. The hair of the animal, the clothing of man, the protection of rooms or other sheltered places, all tend to counteract the full influence of the temperature of the surrounding medium. Man lives, as Rubner well expresses it, everywhere in an atmosphere at a temperature of 32°—that is, the temperature of the air between the surface of the body and the nearest layer of clothing.

Voit (9) also expressly states that involuntary chemical heat regulation in the cold, which he grants does exist within certain limits, is insufficient in the frozen zone. Here man, apart from regulation by clothing, is driven to carry out muscular work in order to maintain body temperatur. Only in so far as the movements are increased are the food requirements greater in cold countries. The same holds for the diminution in activity and amount of food required in the tropics.

The very large amount of food which the Eskimos periodically ta points only to a greater functional capacity of the alimentary canal in the cold, and the abstemiousness of the Arab to a greater endurance of hunger and thirst. The digestive system and the nervous mechanism which controls it are affected both by heat and by cold, and as a result we often eat more in winter than in summer, although the body requirements may be the same. If this be done, then, we store in our bodies a supply of food material which is used up during summer. The energy exchange is the same in summer and winter if the same amount of work is car d out. Eijkmann[1] has proved this in his recent estimations of the gaseous exchange in rest. K. E. Ranke has proved it in another way. He showed that *in order to maintain the body-weight* the same amount of food is required in winter and in summer for a definite amount of work performed. Europeans, during oppressive summer heat, or when in the tropics, instinctively diminish the amount of food in their diet, but the body loses weight in order to furnish the necessary amount of energy [Eijkmann, K. E. Ranke (9)]. The appetite of an individual subjected to high temperatures is more quickly satisfied than when the temperature is lower. Ranke found that if sufficient food were taken in the tropics to furnish all the necessary bodily requirements severe digestive disturbances made their appearance. But these facts do not alter the correctness of the statement that metabolism is the same at high as a medium temperatures. The older investigators were led astray by the effects on the digestive system and on the appetite. No adaptation of the organism subjected to high temperatures is brought about by a diminution in the fundamental metabolism (the energy exchange of the resting organism). The necessary energy expenditure for work is also certainly not diminished. For the same amount of work the heat production is never less during a warm period than during a cold one.

There is no doubt that a native of the tropics has the advantage over a European in India, but the advantage does not depend upon any diminution in heat production. The O_2 intake and the CO_2 output of the Malay and negro stand at the same level as those of the European [Eijkmann,[2] Rubner], and the same is true with regard to the quantity of water evaporated [Rubner (9)]. The negro, however, is able in summer to take a full diet owing to the small amount of protein which he consumes, and also because he is wonderfully free from fat. Perhaps his greater capability of doing work depends upon an earlier establishment of physical

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[1] In winter he found that the O_2 intake was 253·8 c.c., the CO_2 output 232·2 c.c. per minute; while in summer they were respectively 253·3 and 225·5 c.c.

[2] Eijkmann found, calculating for an average weight of 64 kilogrammes, that the O_2 consumption—

(*a*) For a European in Europe during the cold season = 250·3 c.c.
(*b*) For a European in India during the cold season = 245·7 c.c.
(*c*) For a Malay in India during the cold season = 251·5 c.c.

at regulation, and also upon the fact that his secretion of sweat is not ly earlier developed, but is also more regular in character (9).

At the seaside Loewy and Fr. Müller found the gaseous interchange creased in two individuals, but not in a third one. It is probable that e last result is the most reliable (10).

For the effect of Alpine climates, see the following sections.

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(2) ALTERATIONS IN INSPIRED AIR, AND THEIR INFLUENCE UPON GASEOUS AND ENERGY EXCHANGE.

(a) *Respiration of Air Rich and Poor in Oxygen at Normal Atmospheric Pressure.*

"When the combustion of dead organic matter takes place, *ceteris paribus*, the air becomes rapidly purer (*i.e.*, richer in oxygen). the amount of oxygen used up by animals, apart from very slight variations, remaining the same whether pure oxygen be breathed or a mixture of this with a larger or smaller amount of nitrogen."

This dogma of Lavoisier and Séguin, based on careful experiments, received further confirmation from the animal experiments of Reignault and Reizet, Frédericq, St. Martin, Lukjanow, and others (1). Paul Bert and Quinquand alone found a moderate alteration in richly oxygenated air, this consisting, as a rule, in a diminution of the oxygen absorption. Unlike investigators, J. Rosenthal (1) believes that he has observed enormous alterations up to 1,000 per cent. in the O_2 intake when the oxygen percentage of the inspired air was even slightly altered. His experiments lasted twenty to sixty minutes. The CO_2 excretion and the heat production (measured by calorimeter) remained unaltered in his experiments; that is to say, the oxidation in the body pursued its usual course, uninfluenced by the variations in the amount of oxygen absorbed. Part of the oxygen which disappeared in his experiments is to be found in the residual air, as Rosenthal, in agreement with other observers, believes. A small portion is stored in the blood, as the hæmoglobin can combine at a higher partial pressure with some more oxygen. The principal portion of the absorbed oxygen was, however, according to Rosenthal, bound by the living protoplasm as intramolecular oxygen with very slight heat formation, and could gradually be again given off for purposes of combustion. Also, in the case of respiration of ordinary air, there is a similar reserve or intracellular oxygen always stored up in the body, although in smaller quantity than when the partial pressure of the oxygen is high. Thus after exclusion of atmospheric oxygen ordinary oxidation and vital processes can still go on for a short time.

The Intramolecular Oxygen.—Doubtless such a form does exist whether one regard it as loosely bound to the protoplasm, similar to the combination in oxy-hæmoglobin, or more probably as one which permits of a "wandering" of the oxygen.[1]

In excised muscles, and also in uninjured cold-blooded animals,

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[1] Similar to the alternate formation of higher and lower oxidation compounds—as, *e.g.*, in the furnishing of oxygen by cupric oxide or indigo to sugar, and then the taking up of oxygen by the reduced bodies from the air (*cf.* P. Ehrlich's work).

CO_2 excretion and heat production go on for some time after the supply of oxygen has been cut off [Pflüger, Hermann (2)]. P. Ehrlich has investigated, in a series of most ingenious experiments, the subject of the distribution and wandering of oxygen, also the diminution of the oxygen tension in the tissues and in the individual cellular elements. He emphasizes the necessity of inequality of tension to explain the normal course of the processes of combustion (3). Unfortunately his studies dealing with stain reactions have not been made use of in experimental researches dealing with physiological oxidation processes (2).

Respiration in Mixtures of Air containing a Larger Proportion of Oxygen than Normal.

Yet this intramolecular oxygen, the absolute amount of which is unknown, cannot under any circumstances undergo so great an increase in the case of healthy, warm-blooded animals as Rosenthal's experiments appear to indicate. Its amount is not capable of rising to such an extent as to permit a distinct alteration in the course of the normal functions.

This had already been demonstrated for man by Speck (3), who referred the apparently increased consumption during respiration in an atmosphere rich in oxygen to an enrichment of the air in the lungs, and to a physical saturation of the fluids of the body with oxygen. After taking into consideration the circumstances emphasized by Speck, A. Loewy found that the quantity of oxygen consumed was unaltered when the respired air contained as much as 45 per cent. of that gas.

	O_2.	CO_2.
Consumption per minute in ordinary air	220 c.c.	168·5 c.c.
Consumption per minute in air, with 31 to 48 per cent. O_2	210·3 c.c.	171·8 c.c.

Durig has recently furnished us with the most extensive and convincing investigation bearing upon this subject. While making use of all the earlier experimental results, he has precisely demonstrated, with the aid of new and admirable methods, the conditions existing in man. By dividing the investigation into periods of different durations, varying from a few seconds to several minutes, he traced the gaseous interchange from the initial respiration to the conclusion of the first half-hour. It follows from his experiments on men and animals that the quantity of oxygen actually consumed by the organism during respiration in mixtures of air containing a larger proportion of oxygen (30·6 to 80 per cent. O_2) than normal is entirely independent of the supply.[1] It is only within the first three minutes that a certain surplus of oxygen escapes the analysis of the experimenter.

When air containing 73 per cent. of oxygen was inspired there disappeared within the first half-minute 970 c.c. of oxygen, which were not used up in direct oxidation. They served essentially for the replacement of nitrogen displaced from the residual air—*i.e.*, they were utilized for the physical equalization of the composition of the air within the lungs; 260 c.c. of oxygen found entrance into the body in addition to these

[1] And even so during respiration of an atmosphere containing only 9 to 11 per cent. O_2.

970 c.c., which, strictly speaking, were not actually taken up by the organism. Of these 260 c.c., 100 c.c. were absorbed during each of the first two half-minutes, 50 to 60 c.c. during the second and third minutes. After the third minute no further excess of oxygen passed into the lungs or organism. The 260 c.c. of oxygen which are taken up by the organism in excess of that serving for the maintenance of oxidation processes, and are actually utilized by the body, appear, according to Durig, exclusively in the blood, partly in chemical combination with hæmoglobin, partly physically absorbed. No further quantities of oxygen are available for transference into the lymph of the organism, far less for increasing the intramolecular oxygen within the cells.

Consequently a storage of oxygen by the tissues has not taken place.[1] From 200 to 239 c.c. of oxygen are actually devoted to purposes of oxidation during respiration of this atmosphere, containing a high proportion of oxygen—that is to say, exactly the same amount as is consumed in the respiration of atmospheric air.

When a transition is made to the respiration of ordinary air, the surplus of oxygen (1,200 c.c.) which accumulates in the lungs and blood after the respiration of air containing a high proportion of oxygen is first exhausted, and, therefore, affects only for a few minutes the values for the apparent absorption of oxygen—*e.g.*, only about four minutes after a mixture of air containing 48 per cent. of oxygen has been inspired. When the supply of air is entirely cut off, this reserve store of oxygen satisfies the respiratory requirements of a rabbit only for three-quarters of a minute. If rabbits be placed in an atmosphere consisting of pure hydrogen after they have previously been allowed to respire pure oxygen, the onset of asphyxial convulsions is found to be delayed forty-five seconds longer than if atmospheric air had been previously breathed [Falloise (3)].

Respiration of Mixtures of Air containing a Lower Percentage of Oxygen than Normal.

Up to a certain limit a diminution in the proportion of oxygen present in the air breathed is without influence upon the amount of oxygen actually consumed and of carbon dioxide excreted. This lower limit, which is not identical with that necessary for the support of life, is differently stated by different authors from 11 to 8 per cent. O_2 in the inspired air. Down to these values the most careful estimations on the human subject [Speck, A. Loewy, Durig (3)] showed, in agreement with the best experiments on animals, no alteration in the O_2 consumption or in the CO_2 excretion. The transition to respiration of a mixture poor in oxygen is followed by an apparent diminution in the consumption, which only lasts a few minutes[2]—the period required for the establishment of a physical equilibrium between the inspired air and the air already contained in the lungs. On the other hand, a certain surplus of oxygen is consumed in consequence of the necessarily increased work entailed by ventilation, so that the O_2 consumption for this reason frequently exceeds the normal. If one neglect this increased oxidation produced by an alteration in the mechanics of respiration, the minimal metabolism at rest [Grundumsatz] is just as little altered by breathing air poor in oxygen as by breathing that containing an excess of oxygen. Within wide limits the extent of the combustion is independent of the quantity of oxygen present in the air respired. It is rather determined for the cell by laws peculiar to itself [Pflüger].

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[1] Durig has also clearly explained the reasons which led Rosenthal to form his erroneous assumption.

[2] Since the oxygen of the residual air is at first partially used up.

Amount of Oxygen present in the Blood.

During the respiration of air rich or poor in oxygen the composition of the alveolar air undergoes alterations similar in kind to those of the inspired air, but differing in extent according to the character and depth of the respirations. A. Loewy has admirably shown that increased depth in the respirations can prevent a too marked diminution of the partial pressure of oxygen in the alveoli. Under favourable conditions inspired air, containing only 8 per cent. of oxygen, suffices to maintain a proportion of 5½ to 6 per cent. O_2 (=42 to 45 millimetres Hg) in the alveolar air. The O_2 content of arterial blood under these conditions does not sink markedly. Both the blood and the tissues are sufficiently provided with oxygen. On the other hand, when a mixture of air and oxygen containing a large proportion of the latter gas is respired, the amount of oxygen in the blood is moderately increased, essentially as a result of an increased formation of oxyhæmoglobin.

When atmospheric air is respired, the arterial blood is found to contain only 90 per cent. of the oxygen which it is capable of absorbing on being shaken up with atmospheric air, in which the partial pressure of the oxygen amounts to 150 millimetres of mercury. If pure oxygen be respired (partial pressure = 760 millimetres), the arterial blood can take up 10 per cent. more oxygen [N. Zuntz, A. Loewy (4)]. This increased absorption is of no importance for the healthy organism. See the following pages with reference to a possible beneficial effect in diseased conditions.

(*b*) *Respiration of Air having the Normal Composition under Different Barometric Pressures.*

The respiration of air of normal composition, but under altered atmospheric pressure, is subjected to different conditions from those which hold good for the respiration of mixtures rich or poor in oxygen that are respired at the normal atmospheric pressure. In this case we have to deal not only with an alteration of the partial pressure of oxygen, but at the same time with the mechanical consequences of the total alteration of pressure upon the lungs, blood, and entire organism. Climatic conditions are superadded for respiration at high altitudes upon glaciers and in balloons.

Pressure alterations in the pneumatic chamber, whether a decrease to 450 millimetres or an increase to 1,500 millimetres Hg, do not affect the consumption of oxygen either by the human subject or by the dog. This holds good both for respiration during rest and during work [A. Loewy (5)].

The conditions at high altitudes, the problem as to the metabolism in mountainous regions, is of greater practical importance. The consumption during rest is not essentially altered [Bürgi, Zuntz and Schumburg, A. and J. Loewy, L. Zuntz], or may even increase somewhat [Jaquet and Staehelin (5)] up to a height of 3,000 metres, corresponding to barometric pressure of 490 millimetres Hg. The gaseous interchange often rises about 10 to 20 per cent. in the case of lowlanders not accustomed to mountain-climbing, but only in the initial stages of the experiment. This increase, however, is not the result of a diminution in pressure, but rather depends upon other climatic influences to which the organism must adapt itself. Yet this increase in metabolism, which has only been observed by some medical men,[1] cannot be solely explained by an increase in the work done by the respiratory muscles. In the case of L. Zuntz this increased consumption only became manifest at a height of 2,800 metres, while in the case of J. Loewy it only showed itself at a height of 3,600 metres. The increase in the consumption of oxgyen amounted to 80 per cent. upon the summit of Monte Rosa. At this height causes, entirely different from the rarefaction of the air, were undoubtedly the determining factors. Besides, the results obtained are based only on one experiment.

Jaquet (5) found a distinct rise in the gaseous interchange to the extent of about 14·8 per cent. CO_2 and 8·8 per cent. O_2 on the Chasseral (1,600 metres), an altitude by no means great.[2] The respiratory quotient had risen notwithstanding the fact that the mechanical conditions of respiration remained unaltered. It is to be noted with some surprise that the metabolism did not diminish immediately after returning to low-lying ground, but only reached its original height in the course of several weeks.

From his careful and judicious experiments Jaquet concludes that a direct increase in metabolism, outlasting the period of eight days spent at a high level, had taken place as a result of the adaptation of the organism to other climatic conditions. This alteration in the intensity of metabolism also found expression in a change in the composition of the blood. Yet it is not at present permissible to draw general conclusions from Jaquet's results. The experiments of Zuntz and his pupils are at variance with this author's results.[3] The latter have found no constant increase in metabolism even after a prolonged stay at higher altitudes than those at which Jaquet carried out his investigations. Although one may have no wish to deny the therapeutic value of a sojourn at high levels, one must, nevertheless, direct attention to the fact that the increase in metabolism observed by Jaquet was very limited in its extent.

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[1] All these experiments were performed by medical men on themselves.

[2] We here neglect the statements of the authors of an earlier period, which were not carried out with sufficiently adequate methods.

[3] The recent but still unpublished experiments by Zuntz, A. Loewy, and their fellows will decide many an unsettled question (see Literature).

It is not made clear by these experiments whether those who always live in mountainous districts have a higher metabolism during rest than those lowlanders equally skilled in climbing. It is just as uncertain whether the initial increase in the consumption of oxygen is maintained during a permanent stay at higher levels or whether it does not disappear again in the course of weeks or months.

Schroetter and Zuntz found that the actual minimal metabolism at rest was not increased during a balloon ascent at a height of 3,000 to 5,000 metres. The increase in pulmonary ventilation slightly raised the expenditure of work (6).

Some Notes with Reference to the Therapeutic Applications of Oxygen.—Although the inspiration of an atmosphere rich in oxygen does not affect the processes of oxidation in the healthy organism, yet an alteration of this nature may, under certain circumstances, occasionally follow in diseased conditions. The amount of chemically combined oxygen present in the blood can rise from 15·3 to 18·3 per cent. by volume during respiration of pure oxygen. The quantity of physically absorbed oxygen simultaneously increases from 0·3 to 1·8 per cent. [N. Zuntz and A. Loewy (7)]. If the quantity of hæmoglobin present in the blood has sunk during severe anæmia to one-fourth of its normal value, and the chemically-bound oxygen to 4 to 6 per cent. by volume, an increase of the physically-absorbed oxygen can facilitate the provision of the tissues with oxygen. Every increase in the supply of oxygen to the blood plasma and corpuscles is of importance in disturbances of the circulation (cardiac affections). So long as there is no increase in the quantity of blood transmitted per unit of time (a compensatory increase may be of great value in cases of anæmia), a certain gain is obtained even if the same quantity of blood carry with it only an additional 10 per cent. of oxygen. The beneficial effect of respiring pure oxygen is less in cases of extensive curtailment of the respiratory surface than one might at first assume. Yet to a certain extent such benefit can be demonstrated even in these cases. If the supply of oxygen be deficient, the inspiration of pure oxygen may frequently still be of considerable value for other reasons. The dyspnœa often present in such cases and the anxiety felt by the patient lead to convulsive efforts of the respiratory muscles, and to general unrest. In this way the demand for oxygen is intensified to an excessive degree. If the supply of oxygen be rendered more difficult, the oxygen requirements of the patient become not merely abnormal, but are raised far above the normal requirements. Any means for facilitating the absorption of oxygen can break through this vicious circle. The supply of pure oxygen will thus relieve the patient's anxiety and unrest, and in this way decrease the consumption of oxygen by removing the injurious strain[1] (7).

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[1] Morphia also has a similar action in these conditions. In such cases it acts, not only as a palliative or anodyne, but actually as a remedy, which, it is true, does not attack the disease itself or its cause, but nevertheless indirectly, and most effectively, removes one of the most severe consequences.

(c) *Excess of Carbon Dioxide and other Impurities which may be present in the Air breathed.*

An increase of 1 per cent. in the quantity of carbon dioxide contained in the air raises the volume of air breathed to the extent of about 2 litres, an increase of 7 per cent. causes a rise of fully 16 litres, since the accumulation of carbon dioxide in the blood greatly stimulates the respiratory centre. This additional work due to more complete ventilation leads to a rise in the O_2 consumption, which, however, strange to say, is strikingly small. Speck, to whom we owe these experiments, therefore assumes that a decrease in the processes of combustion follows inhalation of air containing 1 per cent. of CO_2. He believes that this decrease may become still more marked if the respired air not only contain excess of CO_2, but at the same time a smaller proportion of oxygen than normal (8). According to Speck, this action does not make itself felt if the quantity of CO_2 sink below 1 per cent. Wolpert confirms this statement at least in so far as one has to deal with pure CO_2. On the other hand, according to the latter author, if the air respired be rendered impure by means of fires or the exhalations of human beings, the O_2 consumption and CO_2 excretion are diminished to the extent of 10 to 15 per cent., even when the proportion of CO_2 present in the air is only 5 to 7 per cent. (8).

(3) INFLUENCE OF MEDICINAL TREATMENT ON THE TRANSFORMATION OF ENERGY.

See the special section by O. Loewi in Vol. III.

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6. Individual Differences in the Minimal Metabolism during Rest ("Grundumsatz").

(1) Influence of Size, Weight, Superficial Area, Composition of the Body, and Constitution.

(a) *Influence of Weight and of the Superficial Area upon the Minimal Metabolism (Grundumsatz).*

The minimal metabolism during rest (*Grundumsatz*) varies in different individuals according to their weight, to the superficial area of their bodies, and to their constitution. In Table I. is reproduced the metabolism of adult males per minute, as determined by Zuntz's method in numerous experiments of one hour's duration [Magnus-Levy and E. Falck (1)]. Only those experiments are included in which absolute muscular rest was sought, and, as a rule, attained (undoubtedly most completely in the experiments on medical men, whose consumption of oxygen was generally lower, and whose rest was more complete than in other persons; see Nos. 2 and 7-12 of Table I. All these experiments were carried out on individuals in a fasting state).

The minimal resting metabolism (*Grundumsatz*) may be deduced from the gaseous interchange during sleep in a manner similar to that stated on pp. 204-205. The quantity of carbon dioxide excreted is stated for periods of six to eight hours in the majority of the investigations emanating from the Swedish school. I have replaced the quantity of carbon dioxide excreted by the heat-factor, which can be deduced from the ratio existing between the quantity of carbon dioxide eliminated and the amount of heat formed during twenty-four hours. The heat eliminated during periods of six hours' duration has been directly estimated by means of the calorimeter in Atwater's experiments, which are specially valuable, both on account of the care with which they were carried out, and by reason of their frequent repetition. Even these numbers derived from the resting metabolism during the night possibly do not yet represent the minimal metabolism during rest, since deep slumber does not always occupy six to eight hours of the night. Minute examination of original papers reveals still lower values in those cases in which the measurements were carried out for periods of two hours (see Table II. on p. 260).

In the following Table III. the values for the metabolism during twenty-four hours, stated in absolute magnitude and referred to the unit of weight, are placed alongside one another. The figures given in Tables I. and II., which were obtained by two different methods, agree very well with one another, if we exclude certain analyses in which the results are undoubtedly too high.

TABLE I.

GASEOUS EXCHANGE PER MINUTE, AND HEAT PRODUCTION IN TWENTY-FOUR HOURS, DURING ABSOLUTE MUSCULAR REST IN THE FASTING CONDITION.

No.	*Name.*	*Age.*	*Height.*	*Weight.*	*Expired Air.*	*R. Q.*	*Per Kg.*		*Per Individual.*		*Calories in 24 Hours.*	*Calories per Hour and Kg.*	*Constitution.*
							O_2.	CO_2.	O_2.	CO_2.			
			Cm.	Kg.			C.c.	C.c.	C.c.	C.c.			
1	Rud.	24	148	43·2	5·6	750	4·53	3·40	195·8	146·9	1,333	1·29	Very small and thin.
2	Dr. Sch.	24	(?)	48·0	—	783	3·68	2·88	176·8	156·4	1,214	1·05	Small, thin; good muscles.
3	L.	30	153	50·8	5·9	826	3·73	3·08	189·4	182·8	1,315	1·08	Small, thin.
4	Rutt.	36	153	53·0	5·5	833	4·14	3·45	219·5	168·2	1,527	1·20	Poor in fat.
5	W.	56	170	56·5	—	766	3·93	2·98	222·0	188·0	1,519	1·11	Poor in fat.
6	B.	32	161	58·0	5·6	760	3·81	2·90	221·2	162·5	1,510	1·08	Normal.
7	Dr. K.	(?)	172	64·0	—	—	—	2·94	—	188·0	1,656	1·07	(?)
8	Prof. Z.	43	161	65·0	4·5	740	3·39	2·50	220·6	162·5	1.498	0·96	Normal.
9	Dr. M. L.	25	167	67·5	5·2	830	3·43	2·86	231·3	192·5	1,608	0·99	Poor in fat; very muscular.
10	Dr. L. Z.	22	167	67·5	—	865	3·43	2·97	231·3	200·2	1,621	1·00	Poor in fat; very muscular.
11	Dr. J.	30	180	73·0	—	—	—	2·41	—	175·6	1,584	0·905	Normal.
12	Dr. Jaq.	34	170	82·0	—	788	2·76	2·17	226·3	178·3	1,556	0·79	Rich in fat; not corpulent; good muscles.
13	Sp.	29	185	82·7	7·0	757	3·60	2·72	297·6 (?)	225·4	2,030 (?)	1·02	Poor in fat; very muscular.
14	Schm.	22	176	88·3	6·9	814	3·30	2·69	291·7 (?)	237·4	2,019 (?)	0·95	Normal fat; very muscular.

TABLE II.

HEAT PRODUCTION IN SLEEP (= MINIMAL RESTING METABOLISM—"GRUNDUMSATZ"), CALCULATED FOR TWENTY-FOUR HOURS.

No.	*Name.*	*Height.*	*Weight.*	*Calories in 24 Hours.*	*Calories per Hour and Kg.*	*Body Surface.*	*Calories per Sq. Metre Body Surface.*	*Number of Days during which Experiment continued.*	*Constitution: Fat; Muscular System.*
		Cm.	Kg.			Sq. M.			
1	Dr. Andersson	188	90·4	1,773	0·82	2,479	715	2	Small amount of fat; very strong.
2	Professor A	(?)	83·5	1,670	0·83	2,353	710	1	Somewhat corpulent; strong, active sportsman.
2*a*	J. C. W.	178	76·0	1,853	1·02	2,209	839	5 (!)	Medium; highly trained.
2*b*	J. C. W.	178	76·0	1,798	0·99	2,209	814	4 (!)	
3	Servant	176	75·6	1,670	0·92	2,201	759	1	
4	Dr. Johansson	180	73·0	1,632	0·93	2,150	759	8 (!)	Slight; medium muscles; little training.
5	Stud. Med.	171	72·7	1,657	0·95	2,145	773	1	
6	Dr. Clopatt	173·5	72·6	1,550	0·89	2,142	724	2	Medium; good muscles.
7	Engineer	190·5	71·2	1,787	1·05	2,115	845	1	Poor in fat; very good muscles.
8	A. W. S.	176	70·0	1,620	0·97	2,091	775	3	Normal; very good muscles, highly trained.
10	E. O.	173	70·0	1,661	0·99	2,091	794	33 (!)	Normal; very good muscles; highly trained.
11	Cand. Med.	(?)	64·9	1,475	0·95	1,988	742	4 (!)	Slight; good muscles; highly trained.
12	J. F. S.	171	65·0	1,445	0·93	1,990	726	9 (!)	Slight; good muscles; highly trained.
13	Cand. Med.	(?)	63·0	1,492	0·99	1,950	765	1	Slight; normal; trained.
14	Dr. Bjerre	174·5	63·0	1,418	0·94	1,950	727	1	Slight; normal.
15	Dr. Sivèn	162·5	62·5	1,431	0·95	1,939	738	5 (!)	Medium; medium muscles.
16	Dr. Bergmann	172	57·15	1,560	1·14	1,836	850	2	Slight; strong.
17	"Dr."	159	54·98	1,590	1·21	1,780	893	1	Thin; (?).

TABLE III.

THE MINIMAL RESTING METABOLISM IN TWENTY-FOUR HOURS.

Weight.	*Metabolism expressed in Calories for 24 Hours.*			*Weight.*	*Metabolism expressed in Calories for 24 Hours.*		
	According to Table I.	According to Table II.	For 1 Kg.		According to Table I.	According to Table II.	For 1 Kg.
Kg.				Kg.			
43·2	1,333	—	30·9	67·5	1,621	—	24·0
48·0	1,214	—	25·3	70·0	—	1,661	23·7
50·5	1,315	—	25·9	70·0	—	1,620	23·1
53·0	1,527	—	28·8	71·2	—	1,787	25·1
55·0	—	1,590	28·9	72·6	—	1,550	21·3
56·5	1,519	—	26·8	72·7	—	1,657	22·8
57·2	—	1,560	27·3	73·0	1,584	—	21·7
58·0	1,510	—	26·0	73·0	—	1,630	22·4
62·5	—	1,431	22·9	75·6	—	1,670	22·1
63·0	—	1,418	22·5	76·0	—	1,826	24·1
63·0	—	1,492	23·7	82·0	1,556	—	19·0
64·0	1656 (?)	—	25·8	82·7	2,030 (?)	—	24·5(?)
64·9	—	1,475	22·7	83·5	—	1,670	20·0
65·0	1,498	—	23·0	88·3	2,019 (?)	—	22·9(?)
65·0	—	1,445	22·2	90·4	—	1,773	19·6
67·5	1,608	—	23·8				

Although individuals of excessive weight have a greater metabolism than those of slighter build, yet the metabolism does not increase in direct proportion to the weight, but less rapidly. Consequently, if we refer metabolism to the unit of weight, it is smaller in the case of heavy than of light individuals.

Nearly constant values of 22 to 24 calories per kilogramme of body-weight are found for persons weighing from 65 to 115 kilogrammes. They sink to 20 calories in the case of heavier individuals, and rise in the case of lighter ones, up to 30 calories in the case of the lightest individuals examined. The total minimal metabolism during rest of a man weighing 80 kilogrammes is only 30 to 40 per cent. higher than that of a man weighing 40 kilogrammes.

The absolute metabolism does not run parallel with the body-weight, but is nearly proportional to the superficial area of the body. Bergmann recognised this fact more than fifty years ago, and Rubner has proved it by means of numerous experiments (2).

Rubner seeks the cause of this proportional relation in the view that the heat loss from the surface of the body determines heat production. This, at all events, does not hold good for cold-blooded animals. Hösslein and Zuntz have given the following interpretation to this law: The metabolism is nearly proportional to the volume and vital energy of the muscles, the mass and development of which increases in the animal kingdom almost *pari passu* with the superficial area of the body (1).

Table II. contains, amongst other data, a calculation of the minimal resting metabolism referred to the unit of surface. If Bergmann's law be strictly valid, then these numbers must be approximately equal. Yet, as a matter of fact, they deviate considerably from one another. This depends, in part, on the fact that the superficial areas were calculated according to Meeh's formula, and not measured in every individual case.

The constant in Meeh's (2) well-known formula (O [*Oberfläche* or surface] = constant $\sqrt[3]{\text{weight}}$) varies, however, from 12 to 12·96 even in the five adults examined by that author—*i.e.*, a variation of about 8 per cent. The superficial area is markedly greater in the case of tall men than in shorter individuals of the same weight. The constant is, therefore, certainly at least 5 per cent. greater in the individual No. 7 of Table II., having a height of 190·5 centimetres and a weight of 71·2 kilogrammes, than in No. 5, who measured only 171 centimetres, but had a weight of 72·7 kilogrammes. If calculated according to Meeh's formula, the result would have been about 1½ per cent. lower. Yet even if this error in the calculation of the superficial area be taken into account, the table shows that the square metre of surface gives off different quantities of heat in different individuals, and it is to be noted, essentially more in the case of small and light individuals than in those of greater weight. Further, the same statement holds good not only for the minimal metabolism at rest reproduced in the above-mentioned table, but also for the actual measured metabolism per diem [*cf.* Eckholm (2)]. In the latter case also the lighter individuals furnished up to 20 per cent. more heat per square metre of surface than the heavier ones.

(*b*) *Influence of Constitution* (*Fat Deposit, Conditions of Muscular Tone, etc.*).

Adipose tissue is essentially a reserve material. Ninety-two and even 95 per cent. of fat with only 5 to 7 per cent. of protoplasmic tissue (containing 3 to 6 per cent. of water and 1 to 1½ per cent. of protein) are present in pure unmixed (?) lard. Adipose tissue is a lifeless mass, and connective tissue has undoubtedly a less intense metabolism than the same mass of muscular or glandular substance. An excessive deposition of fat will, therefore, not increase the absolute metabolism of the resting organism. The foregoing numbers are consequently only directly comparable on the assumption that different individuals harbour within their bodies approximately equal amounts of fat and connective tissue (in the form of fasciæ, tendons, compact osseous material, etc.).

Bischoff and Voit (3) found 12·36 kilogrammes of fat in the body of a sturdy labourer weighing 68·6 kilogrammes; 8·8 kilogrammes of these were contained in the adipose tissue proper, and 3·55 kilogrammes (*i.e.*, 4 per cent. of the body-weight) in the remaining organs. I have calculated, from the figures given by Voit, that men weighing 50 to 76 kilogrammes contain 7 to 13 kilogrammes of fat—*i.e.*, 13 to 19 per cent., or, on an average, 16 per cent. of the body-weight. This may be regarded as the normal proportion of fat. A well-nourished girl weighing 55 kilogrammes contained 15 kilogrammes of fat—*i.e.*, 27 per cent. of the body-weight (3).

A difference of 5 kilogrammes of fat is distinctly noticeable even in the external appearance of the individual, since its deposition occurs in the usual sites of fat storage. If the absolute gaseous interchange remained unaltered, whether this amount of fat be deposited or disappear, —and this assumption appears to us a probable one—then the numbers calculated per kilogramme of body-weight will undergo an alteration of a few percentages—that is to say, an individual in whom a reduction in the amount of fat present has occurred will consume about 5 to 10 per cent. more oxygen than in his previous condition.

One would, therefore, generally expect that fat individuals—presupposing the absence of any abnormalities in their metabolism—would have the same minimal metabolism during rest as healthy ones of otherwise similar constitution (*e.g.*, size, age, muscular development, etc.). The heat formation will naturally be smaller when calculated per unit of body-weight, since the unit of weight has a different composition in the former case, because these individuals contain a larger store of dead material. Magnus-Levy found—

			$C.c.\ O_2$ per Minute.	
	Height.	*Weight.*	*Absolute.*	*Per Kg.*
	Cm.	Kg.		
In the case of an obese individual of ..	167	109	307	2·82
In the case of a healthy individual of ..	175	83	297	3·60

The total consumption of energy during bodily labour must be higher in a corpulent person, since he has a greater weight to move.[1]

Temperament has apparently no influence upon the extent of metabolism in the resting condition. The total daily metabolism must, admittedly, be greater in the case of active individuals of a sanguine temperament than in the case of those of a phlegmatic disposition.

(*c*) *Influence on Gaseous Interchange of Alterations in the Composition of the Organism.*

Permanent alterations involving merely the proportion of water present do not occur in healthy men. A moderate increase or diminution in the amount of fat deposited does not alter the absolute extent of the metabolism (see the foregoing remarks). Variations in the amount of glycogen stored up are likewise without influence on metabolism (see the chapter on Hunger).

In all probability the same statement does not hold good for alterations in the amount of protein present in the organism. It has been proved, by means of numerous observations upon dogs, that an excessive supply of protein increases the quantity of protein in the body, and still causes a rise in the gaseous interchange even after the action upon digestion has died away [Pflüger, Rubner, Magnus-Levy, Frentzel, and Schreuer (4)]. Cases undergoing treatment by means of overfeeding with large protein rations offer the best opportunity of making similar observations on man. The rise in the processes of oxidation which Svenson observed in patients convalescent from typhoid is possibly to be referred in part to the excessive protein diet and to an increased protein metabolism.

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[1] Compare the chapter on Obesity (as well as the section dealing with the rôle played by water in the bodily economy and in heat formation) for a consideration of the special conditions and of possible variations from the normal occurring in obese individuals.

The question as to whether continuous training leads to a rise in the metabolism of the resting organism is one of practical importance. Training certainly produces, along with the increase in the size of the muscles, a much more marked augmentation of their functional capabilities. Is this increased readiness and capability for work shown by the trained muscular system accompanied by, or is it even dependent upon, an increase in the metabolism of the resting organism? This problem has, so far as we know, only once been made the object of an investigation expressly aiming at its solution.

Zuntz and Schumburg (4) found that the metabolism during rest was actually increased in soldiers examined by them at the close of a march of ten weeks' duration, which had led to increased development of the muscular system, with a corresponding decrease in the amount of fat present in the organism. In one case this increase amounted to 6 per cent., in another to 14 per cent.

	P.			*B.*		
	Weight.	C.c. O_2 per Minute.	C.c. O_2 per Kg. and Minute.	Weight.	C.c. O_2 per Minute.	C.c. O_2 per Kg. and Minute.
	Kg.			Kg.		
Average of the first experiments immediately prior to the march	68·8	278·2	4·04	64·2	240·1	3·74
Average of the last experiments at the close of the march ..	66·9	287·8	4·30	63·0	267·1	4·24
		+6½ per cent.			+14 per cent.	

It must be admitted that these estimations do not solve the question as to whether the resting metabolism of an untrained man invariably rises under the influence of prolonged training. We regard the suggested solution as an improbable one. In any case, it is not permissible to attribute a higher resting metabolism to muscular, well-formed men than to individuals of the same weight and size, but possessing a flaccid muscular system. An accurate review undertaken from this standpoint, and including all investigations upon gaseous interchange, both those carried out by others as well as by myself, has proved to me that it is just the most muscular and best-trained individuals who do not show any greater formation of heat in the resting condition and during sleep than individuals possessing a feeble muscular system[1] (*cf.* the statements with regard to the muscular system and its functional capability given in Tables I. and II.). It should also be borne in mind that the "weak" female sex is no whit inferior to the male in the intensity of its metabolism (see the following section). In order to be able to perform a larger amount of work, the animal organism does not require a greater supply of heat when in the resting condition; the greater functional capability of the same muscular mass does not invariably presuppose a more intense resting metabolism.

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[1] The statements referred to which are not expressly contained in the literature are based upon the personal experience of the writer.

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7. Age, Sex, and Race.

(a) Influence of the Period of Life.

Manhood.

Personal experiments by Speck, Zuntz, and several of his pupils, as well as by Johansson, continued for six to fourteen years, demonstrated that the gaseous interchange in manhood remains at the same level as age increases. The individuals examined had reached the third, fourth, fifth, and sixth decennia of life (1).

Old Age.

In old age the gaseous exchange and heat production are decreased; the total metabolism for twenty-four hours diminishes. This, indeed, is to be readily explained by the decrease in vitality and in bodily activity.

Three old people, sixty to eighty years of age, weighing 59 to 66·6 kilogrammes, produced 1,823 calories.

Five young people, twenty-four to thirty-one years of age, weighing 60·2 to 65 kilogrammes, produced 2,136 calories.

The minimal metabolism of the resting organism is also less than in vigorous manhood [Magnus-Levy and E. Falck (2)]. When height and weight were nearly the same, the amount of oxygen consumed by old men of seventy to eighty-six years of age while in the resting state was

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only 73 to 86 per cent. (on an average 80 per cent.); the amount of carbon dioxide excreted was only 82 per cent. of the quantities found in the case of robust individuals of middle age (see p. 268 for further concrete examples). The metabolism may be so lowered that its total for twenty-four hours spent in the respiration chamber does not reach the minimal daily metabolism of more youthful men when in an absolute resting condition. Three old men (Nos. 17, 18, and 20) examined by Eckholm, aged seventy-three to eighty-one years, and weighing 50 to 59 kilogrammes, produced only 1,398, 1,547, and 1,677 calories in twenty-four hours although amply supplied with nutriment. These figures may be compared with those in Table III., p. 261, which represent the consumption of young individuals at rest. The man, aged sixty-two, examined by Buys was also characterized by very low nutrient requirements—namely, 6 to 8 grammes of nitrogen in the form of food, yielding at most 1,700 calories. Yet under these conditions he remained in nitrogenous equilibrium, and maintained a constant body-weight, notwithstanding the fact that he worked for eight to ten hours daily.

Even when calculated per unit of surface the gaseous exchange is found to be about 20 per cent. lower in old age than in middle life (2). This result is opposed to Rubner's view.

Old age, the onset of which is admittedly not limited to a fixed period of life, is accompanied by a general diminution of all the processes of oxidation. The heat loss adapts itself to the altered conditions both by reducing heat conduction and radiation, and by limiting the evaporation of water from the drier skin. The anatomical and physiological alterations of the surface of the body, which provides for the excretion of heat, go hand in hand with a decrease in the formation of heat in the internal organs. Yet the limitation of heat formation is undoubtedly the primary factor, the diminution of excretion playing a secondary part (*cf.* also the statements given on p. 216).

Childhood.

The gaseous exchange in children is much more vigorous than that of adults. The absolute consumption of oxygen at rest is almost half as great in a child of two and a half years, weighing 11½ kilogrammes, as in an adult of six times the weight. It is only slightly less between ten and fourteen years of age, and about the time of puberty children, who are not yet fully grown, produce almost as much heat as adults. The consumption of oxygen, when referred to the unit of weight, is 1·3 to 1·7 times as great in the case of the children examined as in adults [Magnus-Levy and E. Falck]. This indicates that the dietary of children cannot be calculated in relation to their weight. They require a proportionately more liberal diet than the adult, since growth demands a surplus of intake over output. When arranging dietaries for schools, etc., this fact is of much practical importance. On the other hand, according to Rubner, it should not exceed that in manhood, when referred to the unit of surface. According to later researches, this statement does not hold for the resting state. The metabolism per square metre was about 1·1 to 1·6 times

THE GASEOUS EXCHANGE OF CHILDREN [MAGNUS-LEVY AND E. FALCK].

Numbers of		*Weight.*	*Age.*	*Height.*	*Consumption of Oxygen.*		*C.c. O_2 per Kg.*	*Relative Values of Oxygen Consumption for Children and Adults.*[1]			
								Per 1 Kg. of Body-weight.		Per 1 Square Metre of Surface.	
Boys.	Girls.				Boys.	Girls.		Boys.	Girls.	Boys.	Girls.
		Kg.		Cm.	C.c.	C.c.					
1	—	11·5	2½	(?)	112·2	—	9·76	285	—	160	—
2	—	14·5	6	110·0	133·6	—	9·21	269	—	163	—
—	1	15·3	7	107·0	—	125·1	8·19	—	218	—	135
3	—	18·4	6	110·0	139·9	—	7·61	223	—	145	—
—	2	18·2	6½	—	—	135·0	7·42	—	196	—	130
4	—	19·2	7	112·0	152·2	—	7·93	232	—	154	—
5	—	20·8	7	110·0	165·7	—	7·97	233	—	159	—
6	—	21·8	9	115·0	148·0	—	6·79	199	—	137	—
—	3	24·0	12	129·0	—	135·2	5·63	—	149	—	108
—	4	25·2	12	128·0	—	135·0	5·36	—	142	—	105
7	—	26·5	11	129·0	165·5	—	6·24	183	—	137	—
8	—	30·6	10	131·0	192·0	—	6·28	184	—	142	—
—	5	31·0	13	138·0	—	171·7	5·54	—	146	—	116
—	6	35·0	11	141·0	—	187·6	5·36	—	142	—	117
—	7	35·5	14	143·0	—	187·4	5·28	—	139	—	116
9	—	36·1	14	142·0	188·1	—	5·21	152	—	125	—
10	—	36·8	14	141·5	184·3	—	5·01	146	—	121	—
11	—	39·3	16	149·0	194·4	—	4·94	144	—	122	—
—	8	40·2	12	—	—	197·6	4·91	—	130	—	113
12	—	40·0	17	154·0	198·0	—	4·95	145	—	123	—
—	9	42·0	11	149·0	—	211·0	5·02	—	133	—	117
13	—	43·0	14	149·0	220·4	—	5·13	150	—	130	—
14	—	44·3	17	154·0	212·7	—	4·80	140	—	123	—
15	—	57·5	16	160·0	235·6	—	4·10	120	—	114	—
16	—	57·5	16	170·0	242·2	—	4·21	123	—	119	—
Adults { *a*	—	66·7	22–43	165·0	227·9	—	3·41	100	—	100	—
—	*b*	61·7	20–28	160·0	—	234·1	3·79	—	100	—	100

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[1] The relative numbers in these four columns are between children and adults of the same sex; those in the fifth column from the end are between boys and girls.

igher in the children examined by Magnus-Levy and E. Falck than in dults. Children, therefore, produce absolutely more heat not merely or the reason that their superficial area is greater in relation to their eight, but more on account of the increased vital energy characteristic f youth [Sondén and Tigerstedt, Magnus-Levy and Falck (3)].

The following table, which contrasts the metabolism of children, dults, and old people of the same height and weight, and consequently aving the same surface, gives a clear picture of the decrease in metabosm occurring in the three periods of life.

The two last columns of the table show clearly that this decrease is ot dependent upon the weight and the absolute superficial area.

GASEOUS EXCHANGE AT DIFFERENT AGES [MAGNUS-LEVY AND FALCK].

	Age.	*Weight.*	*Height.*			*Relative Amounts of*	
				Absolute.	Per Kg.	O_2 per Kilo.	O_2 per Sq. Metre Surface.
		Kg.	Cm.				
Girl	13	31·0	138	171·7	5·54	112	111
Woman	39	31·6	134	156·6	4·96	100	100
Old woman ..	75	30·3	*circa* 140(?)	128·6	4·25	86	84
Boy	15	43·7	152	216·6	4·97	110	100
Man	24	43·2	148	195·8	4·53	100	100
Old man.. ..	71	47·8	164	163·2	3·42	75	78

(*b*) *Influence of Sex.*

The gaseous exchange in women is not inferior to that in men. The following two tables contain the numbers for the minimal metabolism in the resting state according to Magnus-Levy and E. Falck[1] (4). No difference exists between men and women according to Table II.

Sondén and Tigerstedt found in experiments of two hours' duration that the absolute quantity of carbon dioxide excreted by grown-up women is less, while, on the other hand, it is 10 per cent. greater per unit of weight than in the case of men. It appears strange at first sight that the metabolism of the female should be equal to the male.

If we take into consideration the less highly developed condition of the muscular system, the limited capability for work and for expenditure of energy characteristic of the weaker sex, and also bear in mind the relatively higher proportion of adipose tissue in the female organism, one might almost anticipate the reverse. This fact appears to indicate once more that the mass and training of the muscular system has little influence on the minimal metabolism of the resting organism, and that the extent of surface is, as a matter of fact, a much more decisive factor (4).

It would appear, according to Sondén and Tigerstedt (4), that the male exhibits a more intense gaseous exchange than the female only at the time of puberty. The boys examined by them excreted 31 to 56 per cent. more carbon dioxide than girls of the same age. This holds good only for the condition of rest involved in confinement within doors. Under these conditions, the boys would obviously indulge in much greater bodily movement than the girls. On taking the average of numerous experiments, Magnus-Levy and E. Falck found that boys absorbed only 6 to 7 per cent. more oxygen, and excreted a correspondingly greater amount of carbon dioxide than girls (*cf.* the statements on p. 213).

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[1] In this case, as in that of men and children, I have cited all the individuals examined, in order to furnish as extensive material as possible for comparative purposes, with a view to the elucidation of pathological conditions.

I.—GASEOUS EXCHANGE IN ADULT FEMALES PER MINUTE.

No.	*Name.*	*Age.*	*Height.*	*Weight.*	*R. Q.*	*O_2 Consumption in C.c.*		*Constitution.*
						Absolute.	Per Kg.	
			Cm.	Kg.				
1	B. K.	40	135·0	31·0	825	153·5	4·95	Very small, very thin.
2	G.	38	133·0	32·2	812	159·7	4·97	,, ,,
3	W. Shr.	35	142·0	37·9	760	175·5	4·63	Small and thin.
4	O. K.	25	139·0	39·0	750	197·4	5·06	,, ,,
5	L. Gr.	21	147·0	47·2	810	193·6	4·10	Slightly fat.
6	Gu.	57	(?)	47·4	726	169·5	3·58	,, ,,
x	E. Z.	26	157·0	48·6	839	172·0	3·54	Very slightly fat and muscular.
7	M. W.	20	159·0	49·0	884	191·6	3·88	Normal.
8	H. M.	28	157·0	51·2	818	210·8	4·12	,,
9	Sch.	18	152·0	54·0	824	219·8	4·07	,,
10	M. Kl.	17	156·0	54·0	819	202·1	3·74	,,
y	E. Z.	22	150·5	54·8	(?)	187·6	3·43	,,
z	E. M.	23	162·5	55·8	811	204·6 (?)	3·66	,,
11	E. Spl.	28	156·0	61·3	816	252·7 (?)	4·12 (?)	,, very energetic.
12	L. W.	20	167·0	61·0	817	216·8	3·55	,, energetic.
13	Schr. M.	26	155·0	62·7	782	232·9	3·71	,, very energetic.
14	A. Sche.	22	159·0	68·2	822	232·0	3·40	,, ,, ,,
15	Br. K.	27	169·0	76·5	723	232·4	3·04	Adipose, robust.

Nos. 1 to 15 - Magnus-Levy and E. Falck.
Nos. *x* and *y* - Dr. Leo Zuntz } Personal information ; numerous experiments.
No. *z*, - - Dr. Fr. Müller }

II.—GASEOUS EXCHANGE IN MEN AND WOMEN PER MINUTE [MAGNUS-LEVY AND FALCK].

Women.			*Men.*			*Relative Numbers for Women and Men.*	
Weight.	O_2 per Kg.	CO_2 per Kg.	Weight.	O_2 per Kg.	CO_2 per Kg.	O_2.	CO_2.
Kg.			Kg.				
31·6	4·96	4·06	—	—	—	—	—
38·5 48·7	4·85 4·03 } 4·36	3·66 3·37 } 3·49	43·2	4·53	3·40	96	103
54·0	3·91	3·21	53·4	3·93	3·17	100	101
61·7	3·79	3·05	58·0	3·81	2·90	100	105
68·0	3·40	2·80	66·7	3·42	2·77	100	101
76·5	3·04	2·20	85·5	3·45 (?)	2·71	—	—

The difference between the two sexes is not much greater in old age, the maximum of 11 per cent. for oxygen being reached among the male subjects. Here, again, the greater vigour and less advanced years of the males have considerable influence on their rather higher gas exchange.

For the influence of sexual life on metabolism in the female, see the section on Influence of the Reproductive System on Metabolism. For gas exchange in infancy, see Czerney's and Steinitz's treatise in this book. For the influence of race, see the paragraph above, Influence of Climatic Conditions.

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3. SONDÉN u. TIGERSTEDT: s. Nr. 2.—MAGNUS-LEVY u. FALCK: s. Nr. 2.—RUBNER: s. Nr. 2.

4. SONDÉN u. TIGERSTEDT: s. Nr. 2.—MAGNUS-LEVY u. FALCK: s. Nr. 2.

8. The Actual Daily Metabolic Exchanges with Regard to Work and Food.

The total daily metabolic change is made apparent in the various statements contained in the preceding chapters. Beyond doubt, the extent of such change in any individual depends chiefly on the amount of work, and to a less degree on the nature of the food taken.

The next task is to estimate the amount of energy given out when at rest, at light or heavy work, or when confined to bed, and to show the proportionately small effect of food. The observations on p. 272 were made only on adult men.

The Daily Exchange in Various Occupations.

Rest in the House.—The daily exchange which takes place in normally nourished men at rest in the house is shown in the table on p. 272. With the exception of the three cases 13 to 15, who were badly fed, the subjects were all strong men with no excess of fat.

According to these results, the exchange of muscular men, weighing 70 to 76 kilogrammes, is from 2,100 to 2,400 calories. The only figure exceeding this was shown by von Pettenkofer and Voit's worker, who was busy all day at watch-making—light but skilled labour.

For men weighing 60 to 65 kilogrammes the figures are 1,900 to 2,100 calories, and for those weighing only 53 to 55 kilogrammes about 1,950 calories. A higher figure was obtained by Atwater (No. 13) and Eckholm (*c*), but these persons probably exerted themselves more than the others.

No.	*Weight.*	*Calories.*	*Calories per Kg.*		*Author and Number of Days of Experiment.*
	Kg.				
1	76·0	2,397	31·5	29·7	Atwater (4).
2	75·6	2,108	27·9		Sondén and Tigerstedt (1).
3	73·3	2,198	30·0	31·9	Ranke (2).
4	72·7	2,269	31·2		Sondén and Tigerstedt (1).
5	72·6	2,101	28·9		Clopatt (2).
6	70·4[1]	2,639	37·4		Pettenkofer, Voit (3).
7	70·0	2,278	32·5		Atwater (33).
8	70·0	2,279	32·5		„ (3).
9	65·0	2,136	32·9		„ (9)
10	64·8	1,918	29·6		Sivén (2).
11	63·0	2,043	32·4	35·8	Bjerre (1).
12	60·3	1,880	31·2		Sivén (3).
13	57·2	2,505	43·8		Atwater (5).
14	54·98	1,979	36·0	36·2	Sondén and Tigerstedt (1).
15	52·7	1,917	36·4		Pettenkofer, Voit (1).
					Eckholm—
a	71·4		32·9		5 different persons.
b	63·1		35·8		14 „ „
c	56·3		42·4		4 „ „

No.	*Weight.*	*Calorie Exchange.*	*Author ; Number of Days of Experiment ; Occupation.*
	Kg.		
1	70 (ca. 67)	3,600-3,800	P. u. Voit (3 days); nine to ten hours' wheel-turning.
2	70	3,892	Atwater (42 days); eight hours' cycling.
3	65	3,559	„ (18 „); „ „ „
4*a*	76	5,143	„ (46 „); „ „ „
4*b*	76	9,314	„ (1 day); sixteen hours' cycling.

The Daily Exchange at Work and at Rest in Bed.

At hard work—*i.e.*, nine hours' heavy wheel-turning—the clockmaker observed by Pettenkofer and Voit reached 3,600 to 3,800 calories. Atwater and Benedict found the same figures after eight hours' cycling (about 3,500 to 3,900 calories). This shows a considerable output of energy. The heavy work of a blacksmith, a porter, or a labourer on a mountain farm would no doubt show a higher figure. Rubner estimates it at over 5,000 calories. Atwater found a similar result, estimating the heat exchange in J. C. W., a man in training, at 5,143 calories after eight hours' cycling. These figures would be considerably exceeded after athletic exertions. The highest figure obtained by experiments with the calorimeter was in Atwater's subject, mentioned above, when 9,314 calories was the estimate after sixteen hours' cycling.

But to the practitioner it is of more importance to know the average daily exchange during light housework or ordinary light labour[2] and confinement to bed than that obtained after great physical exertion.

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[1] Voit's figures are from a clothed man.

[2] Wolpert's averages relate to skilled labour of only four hours' duration.

As regards the latter condition, there exist only estimates, not accurate estimations. For a strong man weighing 70 kilogrammes doing various kinds of work the daily exchange appears to be :

1. With hard work	3,500 calories and over.
2. With medium work	3,100 " " "
3. With light skilled work	2,600 " " "
4. With rest in room	2,230 " " "
5. The minimal exchange	1,625 " " "
6. The minimal exchange after food intake	1,800 " " "
7. The " bed "-time—equals the average of 4 and 6	2,000 " " "

In the case of the various workers (1 to 4), which show a total of kinetic energy in excess of that estimated for No. 6 (minimal metabolism plus digestion), the difference is accounted for by physical movements. Movement, therefore, would account for about 200 calories (?) in subjects confined to bed, and for 800, 1,300, and 1,700 calories in those doing light, medium, or heavy work respectively.

The estimation of the energy output in subjects lying in bed depends on the following facts : The minimal metabolism and the dietetic exchange are not decreased in disease, but remain much as in health. I have estimated the output due to muscular exertion in those confined to bed at half the total found by the calorimeter in healthy persons " at rest."

In the following table I have made exactly the same calculations in the cases of persons of various weights as previously made with only one subject. The figures in column A were obtained from numerous experiments ; those in B (minimal exchange and digestion) are obtained from an average of 10 per cent. of the values from which A is calculated. The way in which C is found is stated above.

THE DAILY KINETIC ENERGY USED BY HEAVY MEN DOING WORK OF VARIOUS KINDS.

Weight.	A.		B.		C.		D.		E.		F.	
	Minimal Metabolism.		*Minimal Digestion.*		*Exchange in Bed.*		*Rest in Room.*		*Light Skilled Work.*		*Average Work.*	
	Per Kg. and Day.	Per Day.	Per Kg. and Day.	Per Day.	Per Kg. and Day.	Per Day.	Per Kg. and Day.	Per Day.	Per Kg. and Day.	Per Day.	Per Kg. and Day.	Per Day.
Kg. 40	31	1,240	35	1,400	40	1,600 (?)	42 (?)	1,700 (?)	45	1,800	53	2,100
50	27 to 28	1,350 to 1,400	31	1,550	34	1,700	36	1,810	42	2,000	49	2,450
60	25	1,500	27·5	1,650	32	1,900	36	2,150	40	2,400	46	2,800
70	23	1,625	26	1,800	29	2,000	32	2,230	37	2,600	44	3,100
80	22	1,760	24	1,920	27·5	2,200	30	2,380	35·5	2,850	42	3,400
Approximately under 60 kg.					35	1,500 to 1,900	39	1,700 to 2,100	42	1,800 to 2,400	—	—
" " 60 "					29	1,900 to 2,200	34	2,100 to 2,400	38	2,400 to 2,850	—	—

Leyden's estimate of from 1,500 to 2,000 calories as the amount necessary to maintain the metabolic equilibrium of persons lying ill in bed holds good, according to the table, p. 273, for persons weighing from 40 to 60 kilos. For men over 60 kilogrammes it is rather too low a figure. V. Noorden calculated 34 calories per kilogramme for a man doing no work. This works out fairly well for sick people with an average weight of 60 kilogrammes; for heavy subjects it is rather too low, and for light subjects too high a computation (1A). The above estimate, naturally, only holds good for such illnesses as do not directly affect metabolism, as is the case in most diseases. Where we have to deal with an illness which, on the contrary, does affect metabolism—*i.e.*, pyrexia, Graves' disease, etc.—it must naturally be taken into account, and the figures modified, or, better still, re-estimated.

The Daily Exchange on Various Foods.

The exchange at rest in a room, and with ordinary diet, has been already stated. By ordinary diet is meant food containing an energy-supply equal to the energy-demand of the subject—*i.e.*, about ± 20 per cent., with a nitrogen value of 10 to 20 grammes nitrogen.

DAILY EXCHANGE DURING HUNGER.

	Weight. Kg.	*Calories.*	*Calories per Kg.*	*Author* (2).	*Remarks.*
1. Hunger	76·0	2,397	28·8	Atwater (2)	5 days.
1. Food ..	76·0	2,187	31·5	„	Food contents, 2,519 cal., 16·0 N; 4 days.
2. Hunger	71·2	2,136	30·0	Ranke	3 days.
2. Food ..	73·0	2,226	30·5	„	Food contents, 2,252 cal., 15·0 N; 1 day.
3. Hunger	70·5 (67·0)	2,303	32·6	Pettenkofer & Voit	2 days.
3. Food ..	70·4 (67·0)	2,639	40·0	„	Excess food, 3,210 cal., 22·0 N; 3 days.
4. Hunger	64·9	2,062	31·7	Johansson and pupils (2)	5 days following one another.
4. Food ..	65·7	2,517	38·3	Johansson and pupils (2)	Excess food, 4,193 cal., 27·5 N; 3 days.
5. Hunger	90·4	2,306	25·5	Andersson-Bergmann (2)	2 days following one another.
6. „	83·5	2,194	26·3	Sondén-Tigerstedt	1 day (midday meal 2 hours before the experiment).
7. „	71·2	2,292	32·2	„ „	1 day (midday meal 2 hours before the experiment).
8. „	70·0	2,268	32·4	„ „	1 day (midday meal 2 hours before the experiment, not resting).
9. „	63·0	1,853	29·4	„ „	1 day (midday meal 2 hours before the experiment).
10. „	51·2	1,836	32·4	Andersson - Bergmann	2 days following one another.

The exchange is less during fasting than on ordinary diet—thus, according to Ranke, 100 calories; to Pettenkofer and Voit, an average of 330 calories; and in Atwater's assistant, J. C. W., about 210 calories. In Johansson's subject—a doctor—the difference between the exchange during hunger and when on a rich diet (4,200 calories) was about 400 calories.

This difference must not be ascribed entirely to the smaller amount of food taken—*i.e.*, to the decreased exertion required of the digestive organs—but also to the disinclination shown by fasting persons to voluntary movement (2).

The Exchange on a Diet Poor in Nitrogen but rich in Calories.

In persons resting in the house, and taking a diet containing only a small quantity of oxygen, the exchange for twenty-four hours is rather less than when a diet containing an excess of albumin is given (Ranke, Pettenkofer and Voit). Sivèn does not find any difference. It is not possible to form estimates of the digestion of albumin from these experimental values, or even to draw comparisons between the combustibility of albuminoid material excreted from the body and "dead" albumin, such as is used for food.

The same holds good in observing the higher exchanges which occur on a diet in which the calories and oxygen are obviously above the requirements of the subject (3).

EXCHANGES ON N-POOR FOOD.

No.	*Weight.*	*Caloric Exchange.*	*Calories in the Food.*	*N in the Food.*	*N in the Urine.*	*Author* (1).	*Remarks.*
	Kg.						
1.	72·6	**1,994**	2,859	0	9·2	Ranke.	N-poor food.
	73·3	2,198	2,252	15·0	17·9	„	Usual food.
2.	71·3	**2,290**	2,375	1·3	12·1	Pettenkofer and Voit	N-poor food.
	70·4	2,639	3,210	22·0	18·0	„	Usual food.
3.	59·6	**1,850**	2,477	6·3	5·8	Sivèn	Poor food.
	60·8	1,840	2,479	12·7	11·1	„	Usual food.

EXCHANGE ON EXCESSIVE DIETARY.

No.	*Weight.*	*Caloric Exchange.*	*Calories in the Food.*	*N in the Food.*	*N in the Urine.*	*Author* (1 and 2).	*Remarks.*
	Kg.						
1.	72·9	2,493	2,530	62·2	41·9	Ranke	1,800 gm. meat.
	74·2	2,400 (?)–2,500(?)	?	?	22·4	„	Maximal food.
2.	71·5 (68·0)	2,826	4,150	44·8	26·6	Pettenkofer and Voit	Average of three experiments.
3.	65·7	2,517	4,193	27·5	22·3	Johansson and pupils	Average of 3 days.

The exchange in these experiments was actually found to be some hundred (200 to 300) calories higher than with an ordinary diet. This increase depended partly on better digestive activity, and partly on greater muscular activity. This was certainly so in Case 3, the subject of which had fasted for five days before the experiment; in other cases abnormal movements may have arisen from the discomfort following on overloading the stomach (Ranke).

While knowledge of the physiology of food was yet young, it was thought possible to estimate the needs of a community by taking an average of the needs of individuals. Close investigation has since shown the differences caused by size and weight, age and sex. This marked a stage of the progress in the methods of scientific observation. However, for practical purposes, especially such as concern the food-supply of the people, the differences are not so important as for theoretical purposes. This is especially the case in dealing with the influence of body-weight upon the need of food. Although both exchange and need are least in persons of light weight, nevertheless the total individual combustion does not fall in mathematical proportion to the decrease in weight, but by far smaller quantities. The difference in actual daily exchange in persons of various weights is not so great as was at first expected (see the first table, p. 272). It is particularly noticeable that the minimal metabolism in children from twelve to fourteen years old does not markedly differ from that in adults (p. 268). All these observations only hold good while the subjects are at rest, and this is a point specially to be emphasized. The total loss and the necessary intake of food is chiefly determined by the amount of movement and extent of physical labour undertaken by the individual. Thus it is obvious that the food requirements of a man weighing 70 kilogrammes, although at rest not greatly differing from that of an ill-developed tailor or a lad of fourteen, would become greatly raised under the influence of heavy work.

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APPENDIX.

The Question of "Luxus Consumption."

The striking variations in the total amount of food taken by different people has roused the idea among many of the laity that the man who eats freely is extravagant, and that he who eats sparingly can successfully compete with him.

The enthusiasts of moderation even declare that most people eat too much. According to them, the average man requires far less food in order to maintain his life and full working capacity than he is in the habit of taking. This opinion is even shared by some physicians. It is necessary to test it on theoretical grounds and to inquire into the circumstances on which it is based. We allow, to begin with, that men of equal weight and similar constitution, living under apparently similar circumstances, may show considerable differences in their requirements.

Fluctuations of 10 per cent. more or less than the average may still be within physiological limits. If the output of energy is decreased, still greater discrepancies will be seen, as is shown above. Expressed in figures, it would only be possible to speak of a real reduction of metabolic need if a healthy man, weighing 70 kilogrammes, could meet all his daily needs on a diet containing 2,200 calories—that is to say, with 75 per cent. of the generally accepted 2,500 to 3,000 calories. It cannot be denied that a man who has lost 20 per cent. of his weight by reducing his diet, and has also diminished his output of energy, can also live on two-thirds or three-quarters of his previous intake, but such a question does not arise in the conditions under discussion.

1. Theory.

(*a*) *Influence of "Surplus" Diet on Metabolism.*

The addition of even large quantities of surplus fats or carbohydrates to a diet causes but a slight rise in the energy exchange [Rubner, Magnus-Levy (1)]. Only a portion of the surplus food will be consumed during digestion, the major portion being stored up in the body.[1]

If, on the contrary, an excess of albumin is given, metabolism is stimulated, and this far beyond the requirements of the individual [Rubner, Pflüger, Magnus-Levy (1)]. With human beings, however, we have not to deal with such quantities of albumin as were given to dogs during these experiments. If a man doing no work were to take 175 grammes or 200 grammes of albumin instead of 100 grammes, he would be eating to excess. But an increase of albuminous metabolism does not cause any apparent increase in energy-production.[2]

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[1] According to Pflüger, an increase of nitrogen-free diet has no effect in increasing the exchanges—the whole surplus is stored as fat.

[2] Ranke, Pettenkofer, and Voit found in their experiments that an increase of albumin metabolism of 166 to 260 grammes only resulted in raising heat-production some 200 to 300 calories.

At the same time we find a marked falling-off of energy-production when the total albumin in the usual diet is reduced by half (*cf.* first table, p. 274).

The lack of influence of such reductions is most strikingly shown by the results of starvation experiments [Bidder and Schmidt, Pettenkofer and Voit, Rubner, Zuntz and colleagues, Johansson and Tigerstedt, etc. (2)]. Prolonged fasting leads to decreased metabolism only in so far as it diminishes the total amount of living protoplasm.

The only objection that one can bring forward against the result of these experiments is that an organism cannot have had time in ten or even thirty days to accommodate itself to the altered metabolic conditions. To meet this objection it would be necessary to observe the results of experiments with a greatly reduced diet, lasting over months or even years.

It will be shown below whether this is actually the case or no.

(*b*) *Where could a Reduction in Metabolism be effected?*

Our previous division of metabolic processes into those associated with the "fundamental or minimal" resting exchange and those due to the "functional increment" is one which is eminently suitable for a discussion of this question. The possibility of a diminution in the resting metabolism may be considered, and it may be borne in mind that a possible diminution in the energy expenditure associated with the work of digestion, as well as a decrease in the expenditure entailed in muscular activity, may occur.[1]

We are all familiar with the diminished oxidation that occurs when the functions of the thyroid gland are interfered with, but this is accompanied by obvious signs of serious disease. Some observers have also found a reduction in metabolism in cases of loss of sexual activity. But these conditions do not really belong to the question of reducing the normal metabolism in the healthy.

We are left, therefore, with the three questions mentioned above.

(*a*) *Reduction of the Expenditure entailed in the Work of Digestion.*

The expenditure of energy in the utilization of food-stuffs is small, but unavoidable. In an ordinary mixed diet of 2,000 to 3,000 calories, this expenditure amounts to barely more than 150 to 200 calories—*i.e.*, about 6 to 8 per cent. of the caloric intake. Jaquet and Svenson (3) certainly state that some are able to digest with greater economy than the average man; but even if it were held—contrary to our own opinion—that these figures were unduly high,[2] any possible saving under this heading would be very insignificant.

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[1] This point was first brought forward in the discussion of similar conditions in case of obesity [Magnus-Levy (3)].

[2] Jaquet and Svenson found the percentage of digestion expenditure less than did Magnus-Levy, because they dealt with the intake and output in the case of far heavier subjects. Their subjects, weighing 90 to 126 kilogrammes, showed much greater metabolic activity while at rest than the man of 58 kilogrammes whom Magnus-Levy observed. Nevertheless, they received the same amount of food—*i.e.*, 2,300 calories. The results of these observers do not, however, differ markedly when one remembers, what is undoubtedly true, that the expenditure of oxygen is expressed in proportion to the amount of energy-producing food.

A man taking a diet of only 2,000 calories, and requiring for its utilization 100 calories, or 5 per cent., instead of the normal 6 to 8 per cent., would save about 50 to 100 calories. The amount so economized would have to be considered in relation to a possible fat storage on a normal caloric intake, but even in this respect alone it would not lead to an appreciable reduction.

(β) *Can the Expenditure necessary to Muscular Activity be reduced without affecting the Work done?*

This cannot be possible. The chemical energy expended upon the actual mechanical production of work in ordinary occupations amounts to about 33 per cent. of the total output. This figure is also reached within a short time during the performance of unfamiliar tasks, and is not greatly raised by doing heavy work. One cannot comprehend how the unit of work can be carried out with a smaller expenditure of chemical energy when the energy intake is minimal.

In another direction, however, the possible reduction of the expenditure entailed in muscular activity may be considered. A number of daily and habitual movements which are to a certain extent purposeless could be dispensed with.

A man working on a minimum diet could avoid these, although not without some sacrifice of comfort. There is only one way in which a true physiological saving of muscular work could be effected on a persistently low diet. A man who was thus dieted would shortly lose in weight. If during the whole time he kept his muscles in good condition, the loss would take place chiefly from useless ballast. When he has eventually lost about 6 to 7 kilogrammes of fat, he will have about 10 per cent. less of his own body-weight to deal with.

Then, seeing that a man's work consists more in altering the positions of his own body than in moving or raising weights outside the body, the thin man has the advantage by reason of his own deficiency of ballast. He can thus reduce his work-expenditure up to 10 per cent.; according to available data, it appears that the total output of muscular energy in an average worker is from 1,000 to 1,500 calories. The total saving possible in this way would amount only to 100 to 150 calories.

(γ) *Reduction of the Minimal Exchanges.*

A substantial saving of expenditure cannot be effected in the work of digestion or in muscular activity. Any actual decrease in the total formation of heat must find expression in the minimal metabolism.

It has just been shown that an appreciable saving would be 500 to 700 calories—that is, 30 to 45 per cent. of the minimal exchange—which is about 1,500 calories in a strong man. Such a marked reduction of output would be easy to demonstrate in a subject at rest. On the face of it, this does not seem probable. The following observations bear directly on the subject.

2. The Real Foundations of the Theory of "Luxus Consumption."

(a) *Investigations upon the Minimal Metabolism.*

In no one of the experiments on a large number of healthy men has the gaseous exchange during rest been observed to fall to 20 or 30 per cent. below the average, as should be the case if the theory of a "luxus consumption" were sound. Looking at Tables I., II., III., (pp. 260, 261), the variations above the average are from 5 to 10 per cent., but no more, in persons of approximately the same build and constitution. Further, in the case of the women given in the table on p. 270, each weighed less than 40 kilogrammes, lived in a state of destitution, and stated that they had maintained life on "coffee and soup." In such a case, the metabolic exchange would surely have adapted itself to the reduced diet after so long a time. The absolute and relative figures obtained by estimating the gaseous exchange proved that this was not the case. Only in a few pathological conditions does the total intake and output fall to 50 to 70 per cent. of the normal.[1] But in all such cases it was due either to some temporary cause or to acute illness.

(b) *Details with Regard to Prolonged Light Diet.*

To begin with, we must confine our attention to such reports as are based on carefully observed experiments. The stories of travellers about the spare diet of Arabs and other races of simple habits have always proved unreliable [C. Voit].

Vegetarians, who pride themselves on their moderation, take no less combustible food than the average omnivorous eater [*cf.* Fr. Cramer, C. Voit, Rumpf and Schumm, Caspari-Glaessner, etc. (4)]. Over and over again one of their apostles has tried, for the advancement of vegetarianism, to demonstrate that a small food-supply is adequate and sufficient. One vegetarian, open to conviction, undertook to prove this experimentally, and gave Caspari (5) the opportunity of making careful observations during many months. But although he maintained an exceptional degree of muscular development and power by means of his strenuous exercises, he wasted so persistently while taking a reduced diet that he had ultimately to give up the experiment.

Among scientific writings there are only available three other reports, according to which a reduced dietary has sufficed for the maintenance of life and full activity. Buys records the case of an old man who had taken an exceptionally small quantity of food ever since he was twenty years old. In his sixty-second year he weighed 72 kilogrammes, with a total intake of 1,600 calories and 6 to 7 grammes nitrogen. With this he worked in a factory eight to ten hours daily, and, further, went in for physical exercises. At all events, this was a remarkable case, but Buys' observations, carried out every three days, were not really sufficient to prove that the diet met the man's needs.

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[1] For example, in the convalescent periods of myxœdema.

The fact of nitrogenous equilibrium is not in itself enough. After prolonged reduction of nitrogen metabolism, a deficient calorific intake can be supplemented by drawing on adipose tissue without loss of nitrogen from the body.

Chittenden also seems to hold the view, although he does not expressly state it, that it is possible and not undesirable to reduce the total quantity of food together with the reduction of nitrogen. He states that he works comfortably on a permanent diet of 2,000 calories, and also even when he undertakes considerable physical exertion. Here again, however, there is no proof that the diet taken during this time was sufficient to meet the daily needs of his body. Chittenden's health was undoubtedly excellent, but his weight dropped slowly to 57-58 kilogrammes, and at this weight the diet would in any case suffice for the needs of his laboratory work. The gross intake amounted under these circumstances to 35 calories per kilogramme of body-weight.

The best and most prolonged experiments on this point are those of R. O. Neumann (5). He not only carried out numerous and exact investigations on metabolism, but also estimated his output by carefully weighing all food taken.[1] Dietaries of a total of 2,427, 2,777, and 1,999 calories, a net amount of 2,199, 2,403, and 1,766 calories, maintained his weight unaltered for ten, four, and eight months respectively.

The most remarkable part of his report is the great difference in the requirements in the three experiments, which were, nevertheless, carried out within a few years of each other. An intake of 1,766 calories (25 calories per kilogramme) is extremely small for "a muscular and fairly fat man." Although one is not in a position to point out mistakes and errors in this experiment, it should nevertheless be remarked that Neumann himself, in his numerous experiments on metabolism, has always kept to the usual intake of 35 to 40 calories per kilogramme, and this does not appear to have exceeded the output. Again, in Neumann's experiment on metabolism, which lasted fifty days, we have discovered a surprising fact which is quite at variance with all previous reports.[2]

On this account we should be glad, before accepting Neumann's theory, to have further evidence than that derived from the present empirical standard of metabolic requirements.

Neumann was of the opinion that the body can maintain its weight on diets varying in amount. A man can become accustomed to a spare though sufficient diet, and can maintain the weight for a long time. In support of his statement, he says that one "who lived well in other respects" could partake of a diet over and above what was necessary, and as a result a "luxus consumption" would occur. We ourselves have drawn a comparison between Neumann's dietary and that of Renvall's. The Swedish authority took, under apparently identical circumstances, 50 per cent. more nourishment than did the German worker.[2] But such circumstances are undoubtedly greatly modified by the individual temperament. It is not meant by this that the cells of the active individual give rise to a more vigorous metabolism during rest than those of another; so far "cell-temperament" is not recognised. But the sanguine man, especially when well nourished, is more active, and it is in the physical movements that the surplus of energy-intake is consumed. Animal trainers report many experiences of the kind, and it is beginning to be recognised by those dealing specially with the diseases of children [O. Heubner (6)].

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[1] As his weight was generally about 70 kilogrammes, for simplicity's sake he based all his figures on that weight.

[2] See paragraph, Under-feeding, in chapter on Protein Economy.

These purposeless movements represent a certain "luxus" in regard to the essential bodily economy, but not so far as the health and comfort of the individual are concerned. The apparent "luxus consumption" with an excess of food may not be taken without further evidence in support of the possible reduction below a certain standard.

In matters of biology, one cannot without full inquiry deny or put down as impossible any unusual or striking event. Still more caution is therefore required when dealing with a purely quantitative difference such as that of the "luxus consumption." Although we take up a doubtful and questioning position in the matter, it must be clearly understood that we do not finally deny the possibility of a reduction of the tissue requirements. Not every unexplained detail of this question should be characterized as a lowering of the energy needs. Before placing the essential energy-metabolism on a lower basis, further and more precise researches are necessary, and it is probable that such researches must allow for the considerations here set forth. The recent work of Caspari and that of Fenger form valuable contributions to this question. The figures adduced by the latter point to the possibility of a lowering of the necessary extent of changes; those of the former oppose such a contention (7).

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B.—THE NITROGENOUS METABOLISM.

1. General.

The laws governing the metabolism of nitrogen have been so far drawn from the results of experiments on dogs. In man, whose capacity for nitrogenous food is far less than that of carnivora, the variations of nitrogenous equilibrium are more limited. The laws governing it would be more indefinite were they entirely based upon experiments on man. Consequently this section demands a fuller use of results obtained from animal experiments than do other portions of the subject.

Various Limitations of the Conception of Nitrogenous Metabolism.

Nitrogen metabolism is usually estimated by multiplying the nitrogen contained in the urea excreted by the factor 6·25.

This method is open to dispute on various grounds : a small amount of nitrogen is regularly lost from the surface of the body in hair, nails, epithelium, and sweat ; further, a part of the nitrogen of the fæces, which remains in the digestive fluids and intestinal epithelium, is lost sight of. The waste which must inevitably occur in the taking of food must also be included in the unavoidable output which must be reckoned with.

The nitrogen which is lost through the skin and the intestine, especially in the form of desquamated cells, is but slightly oxidized—*i.e.*, the protein decomposition has contributed but little to energy formation. Yet we here deal with protein which has undergone decomposition and transformation, and, strictly speaking, its amount should therefore be added to that calculated from the urinary nitrogen.

But even ignoring these points, the result obtained by multiplying the nitrogen of urine by the factor 6·25 does not tally with the intake of protein nitrogen. A portion of the nitrogen in food is present in the form of amides or extractives,[1] and therefore has but a slight bearing on the question of assimilation or metabolism of albumin. Yet even the protein of the food is not necessarily entirely reconverted into protein within the body, and the fraction not so converted is consequently to be excluded from " protein metabolism in its more restricted sense." It is quite possible that a dog that uses up 50 grammes nitrogen and 100 grammes fat while fasting might have approximately the same metabolism on being fed with 80 grammes nitrogen and 100 grammes fat, or even on 350 grammes protein on another occasion. Although during a fasting period it lived on 50 grammes protein and 100 grammes fat, nevertheless, on taking food it may, perhaps, in the first experiment, have satisfied its needs with 50 grammes protein and 30 grammes amino-acids and 100 grammes fat, in the second experiment with 50 grammes protein and 300 grammes amino-acids. In the latter case, indeed, it had an intake of 350 grammes protein, but had not disintegrated so much tissue-protein. This cannot be stated as actual fact, but, at all events, the true protein metabolism was less than the total protein disintegrated.

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[1] All these expressions are lacking in precision ; they imply " non-protein-nitrogen." The food of herbivora contains more of these than does the food of carnivora or that of man.

In the light of further research the protein metabolism may be shown to be greater than the amount of protein oxidized in the body, or even than the total protein of the food. As a rule, only those quantities of protein which are irretrievably lost to the organism either as a result of consumption and total oxidation or of wear (epithelium, etc.[1]) are comprised in the phrases "protein disintegration" and "protein metabolism."

Besides this, an extensive change in the chemical composition of albumin takes place in the body. One form of albumin, through a loss or addition of nitrogen-free or nitrogen-containing groups, or even without such molecular changes, passes into another type of albumin. Again, the possibility must be admitted, although as yet there exists no definite proof, that an albumin molecule, after fulfilling certain functions which involve partial disintegration, may acquire the missing group, and be again reconstituted.

This internal protein metabolism, or transformation of protein *per se*, is comparable to the business in the various departments of a great banking firm : in the total balance, in the daily or yearly publication of accounts, the departmental details do not appear. An inquiry into this transformation of proteins will no doubt take place in the future. The physiology of metabolism can only to-day safely control the intake and output, and therefrom draw up a rough balance-sheet.

In these remarks an endeavour has been made to point out the various standpoints held, and the expressions available for their indication. It is desirable from every point of view to distinguish between these expressions, and to fix their meaning once and for always.[2]

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[1] Under this heading would also be considered, in dealing with nitrogenous equilibrium, the output of unoxidized albumin in the excretions of the body—*e.g.*, in the milk, or in pathological excretions of albumin by the kidney.

[2] These may be defined as follows :

1. *The Nitrogen Exchange or Metabolism.*

That is, the total nitrogen output from all sources, except the unchanged residue of food-nitrogen which has never entered the circulation, but including the nitrogen of intestinal secretion, which is occasionally impossible to arrive at.

2. *The Protein Metabolism in the Ordinary and Chiefly Used Sense.*

In the ordinary sense this is about 6·25 times as great as the above. Nevertheless, it is customary to estimate the protein metabolism and the nitrogen metabolism by means of the urea excreted daily to the neglect of other sources of nitrogen output.

3. *Disintegration of Protein.*

This is practically the same as the protein metabolism in the ordinary sense after subtraction of an amount representing the nitrogen contained in the extractives of the food.

4. *The Special Protein Metabolism in the Restricted Sense.*

According to our present knowledge the albumin, after passing the intestinal wall with the tissue fluids, becomes albumin once more, and as such has a part to play in the economy of the body.

To this must be added the albumin which is destroyed in the tissues. [The protein

At first such an attempt would rather lead to confusion than to clearness, since hitherto the nomenclature has been very loosely used. In any attempt made now we must endeavour to obtain a definite nomenclature which, where possible, shall follow precedent, and of which the limits shall be clearly defined. Only here and there in the following paragraphs is any attempt made to separate these ideas. In the main they are applied chiefly in an exposition on "protein," or even more of nitrogenous equilibrium.

In former days the albumin exchange was estimated by means of the urea contained in urine, as put forward by Liebig.

Inasmuch as this method indicates not only the urea, but actually almost all the nitrogen contained in urine, these earlier works are not only useful, but often more reliable than many recent ones. Nowadays, however, in attempting to fix a final average nitrogen equation for intake and output, an exact estimate of the total nitrogen is necessary (chiefly by Kjeldahl's method).

The Position of Albumin in the Animal Economy.

The exceptional importance of albumin in the economy of life is shown by von Mulder by the description of the albuminous substances as the *Proteinstoffe*. Pflüger (1) has assigned to it a "royal" position among food-stuffs. Whereas fat and carbohydrates can be obtained from albumin by decomposition, the opposite transformation does not take place. During starvation albumin is regularly disintegrated. The destruction of living protoplasm can be diminished by the giving of nitrogen-free food, but it cannot be repaired by this means.

We are not in a position to explain how and why certain parts of the animal mechanism become used up, and finally die, while the organism as a whole maintains its working power as a unity. It is certain that cells do break down *en masse*—as, for example, the epithelial cells, which

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metabolism in the restricted sense is therefore less than that included in the term "protein exchange" or "metabolism" in Section 2, and also less than the protein disintegration in Section 3.

5. *The Transformations of Proteins per se within the Tissues.*

This includes all those molecules which, while maintaining the character of an albumin, undergo changes in the body.

This quantity is probably considerable even disregarding the primary synthesis of the albumin of food which always decreases on fasting, and the change of serum albumin into the albumin of the tissues. The expressions "protein decomposition" and "protein disintegration" are not free from objection, inasmuch as they really only indicate a breaking down, whereas both disintegration and oxidization should be utilized, since in this connection they almost invariably accompany one another. The expression "protein decomposition" is generally used to indicate the loss of albumin from the tissues. In this sense it could, properly speaking, only be applied to the excess of loss over gain, as part of the albumin destroyed in the tissues is replaced by albumin taken in the food.

It is almost impossible to give good English equivalents for many of the newer German expressions, the difficulty being enhanced by the present confused condition of the English nomenclature. As a uniform terminology has not yet been adopted, a compromise has been effected by the definite use of such words as "protein," "nucleo-proteins," "peptides." The translation of compound terms is frequently made in the context rather than expressed in precise definitions.

cover the external surface and line the different mucous membranes. Still, the principal part of the protein broken down during starvation does not arise from the complete disintegration of a small number of cells, but rather from the partial discharge of the contents of all, or at least of the vast majority, of the cells of the organism. It is much more a question of the diminution of the volume of the cells than a decrease in their number. It is possible that the protein molecule itself has a limited duration of life,[1] just as the cell and the organism, and that the vital processes are intimately related to the life limit of the chemical molecule.

It is only in a few isolated cases that we can recognise any purpose subserved, or any advantage gained, by this protein disintegration. For instance, the hæmoglobin must continue to break down in starvation in order to maintain the supply of bile-pigment. According to Landergren (2), part of the disintegrated protein serves to supply necessary carbohydrate to the organism ; but, after all, we know little or nothing with certainty as to the causes of such protein disintegration, or the purposes which it subserves.

In the first place, the body seizes upon the protein to cover its requirements so far (and this qualification is difficult to formulate)[2] as the protein is presented to the organism in such a form that it easily undergoes disintegration. In the second place, carbohydrates are seized upon, and only at the last are the fats made use of. This preference for carbohydrates over fats has been explained by the solubility and less stable character of the former, due to their aldehyde natures. The same hypothesis has been brought forward to explain the protein disintegration. To their decomposition products, as well as to the protein, has been ascribed a greater tendency to breaking down,[3] although this can scarcely be greater than that of the carbohydrates, when one bears in mind how resistant the former are to oxidation by chemical means. The weightiest grounds for the selection of one food-stuff before another are to be sought, not only in the chemical constitution of the substance, but rather in the general or cellular organization. The chemical process depends upon the interchange between food and cell, and so long as the organization of the protoplasm is unknown we shall not be in a position to explain satisfactorily the unequal stability and the varying degrees of resistance to oxidation offered by substances in the organism.

The order in which the different food-stuffs are stored in the organism is the converse to that which holds for disintegration. Fat is stored most easily and almost to an unlimited extent. The storage of carbohydrates can take place almost as easily, although only up to a definite limit, any excess beyond this being stored as fat. An increase in protein storage takes place only with difficulty, and also to the most limited extent. This appears of advantage, because a marked increase in the amount of living protoplasm cannot certainly be always regarded as a gain to the organism (see the section on Protein Forced Feeding). Still, merely to point out the advantages of a process is not the same as to explain its cause.

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[1] The protein molecule, just as the cell and the protoplasm, can transmit and hand down its form and specific energy to a newly-formed molecule. Its form is constant, while its contents, the C, H, N, and O atoms, may alter. One part of the problem, dealing with the transmission of vital properties—in fact, a most important because a fundamental one—is the transmission of the protein molecule.

[2] So far as our knowledge goes there is at present no definition of this limitation to which exception may not be taken. The above-mentioned one is merely a description.

[3] Perhaps the greater ease with which protein and amino-acids undergo decomposition in the body is due, in the first place, to the facility with which the N is given off. After this has occurred the oxy-acids remain, and these are certainly more readily oxidisable than the fatty acids of the fats.

Labile and Stable Protein (Voit's "Circulating and Tissue Proteid").

"In the first place, the body makes use of the proteid to cover its requirements so long as it is presented to it in easily decomposable form." This statement requires explanation. The protein which is most readily broken down is that which is being continually taken in as food[1] and absorbed by the organism, either as resynthetized proteid, or in one of the many forms of decomposition products, only a proportionately small part being derived from the protein already in the body. By far the larger amount of the body protein is protected from immediate combustion, only a very small fraction undergoing disintegration, and then being replaced by the food which has been taken [C. Voit (3)].

It is still unknown whether the difference which proteins exhibit in their power of resisting disintegration is due to chemical differences or not. There is the possibility that the "living proteid molecule,"[2] as Pflüger and Loew (4) have always maintained, has a different constitution[3] from the "dead proteid" of the food, such as is analyzed by the chemist, and that the protein which is firmly bound in the organism differs from the easily decomposable variety. Perhaps those parts of the protein molecule in the former, which are, as a rule, attacked by oxidizing or disintegrating agents, are so arranged that they are protected from their influence. Organic chemistry presents analogous cases, and affords grounds for such a hypothesis. Perhaps, however, this is not the case, and no such chemical differences do exist. If this be so, then only that portion of the protein undergoes decomposition which is, for the time being, not essential for vital processes, but only exists as surplus material. Such a teleological conception might then be explained chemically by regarding the surplus protein as not participating in the actual organization of the cell, and not being firmly bound, for example, in its nucleus. At most, it could be regarded as combined only temporarily by means of a side-chain, so that it might easily undergo oxidation. According to this conception of the protein, its inclusion in a more complex molecule would protect it from decomposition for a certain and perhaps prolonged period. A similar condition is seen in the case of chloride metabolism in starvation, where the larger part appears to be firmly bound, although—at least, up to the present—we have no knowledge of a firm chemical combination in the organism.

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[1] With the exception, of course, of those portions which serve to replace stable or labile tissue protein, and are therefore protected from disintegration for a more or less prolonged period.

[2] Here, just as on p. 75, the expression "living proteid" is taken from Pflüger, who has for many years attached special significance to differences in its chemical structure compared to dead protein. If one wishes to emphasize specially the active chemical properties of protein in the organism, one must speak of "the protein molecule in the living protoplasm" rather than "living proteid." [See E. Buchner's description (4).]

[3] Although this possibility is here referred to, it by no means follows that the special views which these authors hold as to the structure of the proteid molecule are true. In fact, it is more probable that they are not correct.

Voit has termed that variety, which is least readily decomposable, "tissue proteid," the easily decomposed form "circulating proteid."[1] These terms he employed under the belief that the proteid in the organs is morphologically more independent, possesses a firmer constitution, and, above all, has a more complex chemical structure than that present in the circulating fluids. He attempted to define their localization as well as their different properties against decomposing agents. This attempt led to difficulties and contradictory results, as Pflüger's thorough analysis of the subject has shown most clearly (5). There is no doubt that both classes of protein are present in every part of the body—in every cell, in the blood, the lymph, and the intercellular fluids. Still, it is advisable to hold to the most important element in Voit's theory, the fundamental difference between the two classes of proteins being expressed shortly and clearly. Hofmeister introduced, during the course of a lecture which he delivered, the terms "labile" and "stable proteid." Naturally, the degree of stability is not an absolute one. As these expressions, however, do not definitely fix the localization of the two classes—nor do they bind those who use the terms to any definite view as to the chemical constitution—they will be used in the following pages. The substitution of these terms for those used by Voit, although Pflüger was right in objecting to the deductions from the theory of the latter, serves to retain the essential elements in the view of Voit.

LITERATURE.

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2. Landergren: U. die Eiweissumsetzung des Mensch. Sk. Ar. P. **14.** 112. 1903. s. p. 147.

3. Voit: Phys. des Stoffwech. **1881.** s. p. 300 ff. See also p. 103 ff. and 387 ff.

4. Pflüger: Die phys. Verbrenn. in den lebenden Organismen. Ar. P. M. **10.** 251. 1875.—Pflüger: Einige Gesetze des Eiweiss-stoffwech. Ar. P. M. **54.** 339. 1893.—Loew: Chemis. Energie der lebenden Zellen. **1897.**—Ar. P. M. **79.** 577 ff. 1900.—Buchner: Z. p. C. **44.** 227. 1905.

5. Pflüger: U. einige Gesetze des Eiweiss-stoffwech. Ar. P. M. **54.** 339 ff. 1893.

2. Protein Metabolism in Starvation

The usual order will be here adopted of treating the protein metabolism in starvation as introductory to the general treatment of protein metabolism. Many of the most important features in the metabolism of protein are to be observed in the study of the metabolism of starvation.

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[1] It is an obvious transition to transfer the idea "easily decomposable" to the main mass of protein derived from the food.

It is of special importance in the theoretical discussion of metabolism to observe that the nitrogenous metabolism practically corresponds to the actual protein metabolism.[1] About 90 per cent. of the nitrogen of muscles and of the glands is in the form of protein, 10 per cent. as extractives, while in the blood the protein nitrogen forms about 99 per cent. of the total nitrogen.[2] As the ratio of protein to extractive nitrogen in the tissues does not with any certainty markedly alter during starvation, certainly 90 per cent. of the total nitrogen excreted during starvation is derived from the protein katabolism.[3]

During the days first following the withdrawal of food the protein metabolism is directly dependent upon the protein intake and decomposition during the preceding days. The amounts of labile protein present in the body are directly dependent upon the quantity of protein taken during the preceding days, and it is this labile protein which is practically completely used up during the first three or four days of starvation. If the quantities taken beforehand be large in amount, the nitrogen output during the first days is high, and if they be small, the output is correspondingly low. In the same dog Voit (1) showed that the amounts of protein decomposed were the following :[4]

	After Preceding Protein Intake, which was		
	Large.	*Moderate.*	*Small.*
	Grammes.	Grammes.	Grammes.
On 1st starvation day ..	175	77	40
„ 2nd „ „ ..	72	54	33
„ 3rd „ „ ..	56	46	30
„ 4th „ „ ..	50	53	36
„ 5th „ „ ..	36	43	35
„ 6th „ „ ..	39	37	37

From the third to the fourth day of starvation the nitrogen excretion is almost constant in amount, and subsequently falls very slowly.

If, as Voit has said (2), about 8 per cent. of the stable protein and 70 per cent. of the labile protein of the organism are decomposed during starvation, then the latter must be used up completely within three days. After twenty-four hours of starvation only 30 per cent. of the labile protein present before withdrawal of food remains within the organism, after forty-eight hours only 10 per cent., and at the close of the third day only 3 per cent. is found. Voit's classification, therefore, may be regarded as correct, so far as one can judge from the rapid fall in protein katabolism during the first days of starvation and its constancy in the later ones. From the fourth to fifth day onwards only stable tissue protein remains for oxidation, the labile having disappeared.

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[1] The term " protein " is obviously used here in its widest sense as including gelatin nucleo-proteids, etc.

[2] If one neglect the analyses of muscle and of blood, no large number of systematic investigations dealing with the quantity of extractives in the organs are available. (Compare the section on Overfeeding with Protein for further details.)

[3] In all probability, however, those extractives are themselves derived from tissue protein, for they are, at all events, only in part absorbed as such from the food. At the same time it is impossible to decide whether they have first arisen through decomposition of an originally intact protein molecule, or whether they have been directly synthetized from decomposition products of the protein of the food without the formation of such intermediate substances.

[4] Voit gives the numbers for urea. I have calculated them in terms of protein.

In man, the initial fall in protein katabolism during the first days of starvation is less marked than in the dog, because the protein intake in the former never reaches such a high absolute standard as in carnivora. The close relationship between this fall and the metabolism on the preceding days is, however, also recognisable in the case of man, as the following extract from the experiments of Prausnitz (3) shows:

			The Same Person.		
Subject:	1	2	5	6	15
Weight (*Kg.*):	41·7	45·0	60·6	60·6	118·8
Urinary N on the 1st normal day	11·7	6·4	9·6	8·5	22·3
Urinary N on the 2nd normal day	9·3	8·1	12·0	7·8	23·1
Urinary N on the 1st hunger day	7·8	4·6	13·3	9·9	17·3
Urinary N on the 2nd hunger day	13·0	4·4	11·0	10·3	19·3

The smaller the nitrogen excretion on the normal days, the lower the nitrogen output also during the subsequent period of starvation. In some cases more nitrogen is excreted in the first day of starvation than immediately preceding this.

In many cases the protein katabolism in man increases on the second day, but often only on the third or fourth day of starvation (see the above table). Prausnitz, who noticed this first of all, and after him Landergren (4), have explained this by referring it to the disappearance of the glycogen of the body (see also p. 312). The carbohydrates stored in the body act in the same way as those in the food—namely, as protein sparers. On the second or third fasting day they are practically exhausted, and, as a result, the protein metabolism temporarily rises.

After these initial variations the protein katabolism in man gradually falls during the course of starvation. In the first ten days the nitrogen excretion seldom falls below 10 grammes, but then later on slowly falls still lower.

Succi, in a healthy condition (weight about 55 to 57 kilogrammes), excreted from 6 to 3·2 grammes nitrogen on the twentieth to thirtieth day of starvation. The excretions in chronic inanition became still less. In such cases the functional activity may be markedly lowered, the weight sinking to a minimum. The following examples may be quoted (6):

	Weight in Kilogrammes.	*Nitrogen Excretion in Urine.*
Senator	35	1·8
Nebelthau	40	2·3
C. Voit	> 34	about 1·0

NITROGEN EXCRETION IN THE URINE DURING STARVATION IN MAN (LANDERGREN[1]).

Hunger Days.	*Schreiber and Waldvogel.*		*Landergren.*	*Keller.*	*Johansson.*	*Breithaupt.*	*Cetti.*	*Luciani.* Succ.	*Freund.* Succ.
	I., ? Kg.	*II., ? Kg.*	78·0 *Kg.*	*? Kg.*	67·5 *Kg.*	59·9 *Kg.*	56·5 *Kg.*	*I.,* 62·4 *Kg.*	*? II., Kg.*
	Gms.	Gms.	Gms.	Gms.	Gms.	Gms.	Gms.	Gms.	Gms.
0	7·15	(?)	19·7	(?)	23·4	13·0	13·5	16·2[2]	(?)
1	8·8	9·5	13·6	8·2	12·2	10·0	13·6	13·8	17·0
2	10·1	11·4	13·4	6·8	12·9	9·9	12·6	11·0	11·2
3	11·7	14·3	15·1	7·9	13·6	13·3	13·1	13·9	10·6
4	—	—	13·9	11·5	13·7	12·8	12·4	12·8	10·8
5	—	—	—	—	11·5	11·0	10·7	12·8	11·2
6	—	—	—	—	—	9·9	10·1	10·1	11·0
7	—	—	—	—	—	—	10·9	9·4	8·8
8	—	—	—	—	—	—	8·9	8·4	9·7
9	—	—	—	—	—	—	10·8	7·8	10·0
10	—	—	—	—	—	—	9·5	6·7	7·1
11–15	—	—	—	—	—	—	—	5·8 (3·5–7·9)	4·7–6·8
16–20	—	—	—	—	—	—	—	5·3 (3·9–6·2)	3·3–5·7
20–25	—	—	—	—	—	—	—	4·7 (3·2–6·0)	(21 days) 2·8
26–30	—	—	—	—	—	—	—	5·3 (4·1–6·6)	—

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[1] See Literature, No. 5.

[2] The numbers in this series are too low (hypobromite method).

Almost all the foregoing statements concerning the excretion of nitrogen in starvation deal only with the figures for urinary nitrogen. At the least the loss of nitrogen in the fæces must be added thereto in order to obtain the actual amount of nitrogen lost by the organism. The nitrogen loss in the human fæces, however, only amounts to 0·5 to 0·2 gramme per day.

Further, it appears from the numbers given in the chief table that only a small quantity of "labile proteid" circulates in the human organism under ordinary nutritive conditions. According to Voit's method of expressing the fact, this amount is equal to the equivalent excess of the proteid metabolism on the first two or three days of starvation above the average of the succeeding days. Such an excess is scarcely anywhere to be found on reviewing the results given in the table on p. 291. Only in Succi's second series does the excess amount to 6 to 7 grammes nitrogen = 40 grammes of protein.[1]

As a rule, the larger organism decomposes an absolutely but not a relatively greater amount of protein during prolonged starvation than the smaller one. Similarly, the young organism decomposes more protein than the old, and the lean organism disintegrates more than the fat one.

A lean dog, weighing 8·88 kilogrammes, which was examined by F. A. Falck, excreted a daily average of 3·9 grammes nitrogen from the second to the seventh day of starvation. A dog with an abundant deposit of fat, which weighed 21 kilogrammes, excreted only slightly more nitrogen—namely, 4·55 grammes—during the day. The greater amount of fat stored, the less is the amount of protein decomposition, and the death owing to starvation is consequently delayed. Falck's lean dog died from inanition after twenty-four days. Its deposit of fat was completely exhausted. The fat animal died after sixty days of starvation, and a similar animal which was investigated by Kumagawa (7) only died after 100 days of starvation.

Periods of starvation lasting thirty days, during which practically nothing was taken except water, have been repeatedly and accurately studied in the case of the human subject, yet no threatening symptoms have become manifest even at the close of the experiments.

Only a small part of the metabolic requirements during starvation is satisfied by tissue protein. This proportion amounts to 15 per cent. in the dog, and to somewhat less—namely, 10 to 12 per cent.—in man. The fat of the body covers the greater part of the expenditure of energy. The greater the amount of fat stored, the greater also is the part played by it in the fulfilment of the energy requirements of the organism.

The quantity of nitrogen excreted during starvation first rises a few days prior to death. The amount of fat present in the body is markedly reduced, the oxidation of the small residue of fat becomes difficult, and in consequence more protein is now oxidized [C. Voit, Rubner, E. Voit, and others]. N. Schulz has adduced further reasons for this "premortal rise in the nitrogen excretion." He suggests, amongst other causes, a primary injury to the protoplasm of the cells consequent upon prolonged starvation resulting in " a protracted death of the cells." Yet his views have with good reason been contradicted by Voit's school [E. Voit (8)]. The dependence of nitrogen metabolism on the amount of fat stored is not only an obvious conclusion from the results of numerous early experiments, but has also been demonstrated beyond doubt by more recent investigations, amongst others by those in which fat was administered subcutaneously to fasting rabbits [Koll (8)]. It is only at the very close of life, during the last few days, that the quantity of nitrogen excreted again sinks.

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[1] On the other hand, 150 to 200 grammes of labile protein may be stored up in the organism of a dog of half the weight as the result of a very abundant meat diet, and then undergo disintegration within the first three days of fasting.

The onset of the latter period, during which the protein undergoes decomposition at an approximately uniform yet slowly diminishing rate, has been of predominant importance in the history of experimental research. This period is well fitted for the study of the influence of food, the action of drugs, poisons, etc., or of the effects produced by different forms of bodily work, muscular work, etc., upon the metabolism of the proteids. As v. Noorden states, sudden alterations in the extent of protein decomposition may, without hesitation, be referred to the influence of the experiment. It is true that experiments in which nitrogenous equilibrium is maintained on a constant diet are to be preferred for the solution of many problems, yet they are not applicable to the solution of others, since the experimental procedure often leads to a refusal of nutriment, and consequently to a disturbance of nitrogenous equilibrium —as, for instance, in those cases in which the action of a poison is being investigated.

Panum was the first to recognise the importance of the " starvation method." Storch (9), while working under his direction in 1865, found a great increase of protein decomposition as a result of phosphorus-poisoning. At a later date this experimental method has proved extremely fruitful for experimental pathology and toxicology in the hands of the Munich scientists and of many other investigators.

The quantity of nitrogen excreted by a fasting animal by no means represents its minimal nitrogenous metabolism. It can be considerably reduced below the fasting values by the administration of large quantities of carbohydrates and fats. Thus the quantity of nitrogen excreted in the urine by a man in a state of starvation is rarely less than 10 grammes, whereas the excretion of nitrogen may sink to 6 or 5 grammes, or even less [Landergren (10)], when an abundant supply of carbohydrates and fats is given. It is true that the nitrogen excreted in such cases represents a loss of nitrogen by the organism. Man can, however, in many cases maintain himself in nitrogenous equilibrium with the foregoing small quantities of nitrogen. In other words, he can keep the protein store of his organism unaltered in amount on a supply of protein which lies far below the amount decomposed during starvation (*cf.* p. 299.)

sumption, which may, with a rise in the intake, reach to ten or fifteen times the normal, have occasioned much uncertainty so long as the degree of the metabolism is regarded purely from the standard of the protein metabolism.

It was from considerations such as these that the theory of "luxus consumption" arose, but we cannot in this place refer to the various presentations of this theory, neither can we here make use of even any portion of this theory, the correctness of which may be assured. But the aberration in the protein metabolism within the limits of Pflüger's law is only an apparent one. As a matter of fact, it is simply a case of a preference for one food-stuff over another, such as is frequently met with in metabolism. With the increased consumption in protein there is a lessened consumption of other food-stuffs. The total energy-metabolism is only raised to proportionately a small extent when nitrogen-free substances are replaced simply by protein. But it still remains a remarkable fact that the organism, in order to supply its requirements, can make use of such varying quantities of protein. It appears much more natural to expect that the protein requirements should only vary within narrow limits. Perhaps the difficulty of explanation might be got over if the hypothesis were found to be a correct one that the food protein is only actually in small part transformed into true protein within the body, or that it only plays the part of protein within the organism to a small extent. Perhaps this property of the organism to adapt itself to such varying quantities of protein signifies nothing else than that the tissues are able to set free the nitrogen of the surplus protein or its forerunners in the form of ammonia. The organism would then make use of the substances which remain—the oxy-fatty acids and similar bodies, which are not unlike the probable decomposition products of the fats and carbohydrates. When it is said that the body is able to burn up all the protein that is given to it within the twenty-four hours, the statement goes beyond what we actually know to be the case. All that is certain is that the nitrogen (and the sulphur) are excreted within this time; but we do not know whether the carbon which is excreted during this time actually arises from the protein or from other sources, nor whether, should it be from the latter, the carbon of the protein is stored in the body in any particular form. It is probable that the former is correct, because, as a rule, bodies of small molecular weight, such as amino-acids, etc., are completely burned up as soon as decomposition and oxidization has once commenced. It is also believed that the oxy-fatty acids which arise from the amino-acids more easily undergo oxidation than the unoxidized fatty acids, and much more easily than the higher fixed fatty acids. Practically, we must regard nitrogenous equilibrium as established when the nitrogen intake and output only vary to the extent of a few decigrammes. The unavoidable errors in technique account for such an error. When nitrogenous equilibrium is actually established, the nitrogen output by urine and fæces, which are alone estimated, ought to be a few decigrammes below the intake, owing to the loss in the sweat and from desquamation of epithelial cells, as well as the small amount required for hair and nail growth. This might at least account for the small difference in the nitrogen balance. It is unnecessary to give accurate estimations.[1] Also in cases where nitrogen is periodically lost, such as in semen, during menstruation, etc., protein must be retained during the intervals to replace the loss, just as for the growth of hair and nails. Bunge (2) draws attention to this in his description of the processes of growth in youths.

The way in which the body strives to adapt the protein decomposition to the intake may be best studied in cases where varying amounts of protein are added to a diet which is almost sufficient for the body requirements. If the protein ration be not raised or lowered to an exaggerated degree, some days elapse before the nitrogenous equilibrium of the organism becomes again established under the altered intake. When the intake is raised, at first a part of the protein is stored, and then in three to four days the body decomposes the whole or almost the whole of the surplus. The following experiment on man shows this distinctly [v. Noorden (3)]:

	Intake.	*N in Fæces.*	*N in Urine.*	*Balance.*
On the 1st day ..	14·4	0·70	13·6	+0·1
„ 2nd „ ..	14·4	0·70	13·8	−0·1
„ 3rd „ ..	14·4	0·70	13·6	+0·1
„ 4th „ ..	20·96	0·82	16·8	+3·34
„ 5th „ ..	20·96	0·82	18·2	+1·94
„ 6th „ ..	20·96	0·82	19·5	+0·68
„ 7th „ ..	20·96	0·82	20·0	+0·14

On diminishing the protein intake the opposite occurs, namely, a moderate loss of nitrogen:

	N in Urine.	*Protein Decomposed.*	*N in the Body.*
On the 1st day	18·2	113·7	−2·18
„ 2nd „	17·0	106·2	−0·98
„ 3rd „	15·8	98·7	+0·22
„ 4th „	16·0	100·0	+0·02
„ 5th „	15·7	98·1	+0·32

In both cases the caloric value of the diet was adequate (3).

Under the usual conditions, when the amount of food taken varies from day to day with the appetite and other external influences, nitrogen loss and nitrogen gain often succeed one another with very short intervals, the result being that, as a rule, nitrogenous equilibrium is maintained for long periods if the diet be a sufficient one.[2] This v. Noorden has verified in an experiment upon himself. The maintenance of the body-weight depends upon the fact that the food intake, as regulated by the appetite, corresponds in the long run to the bodily requirements. In experiments of long duration on man nitrogenous metabolism is by no means so uniform on a constant protein and caloric intake as is the case with the dog [see R. O. Neumann, Rosemann, and Clopatt, as described later on (4)]. Occasionally there are variations of some grammes from day to day. In one of Rosemann's (5) experiments the differences amounted to 10 grammes nitrogen. Rosemann has accounted for these differences, though on insufficient grounds, by a temporary retention and subsequent washing out of the end-products of nitrogenous metabolism.

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[1] For nitrogen losses in the sweat, see the section on the Influence of Muscular Work.

[2] Many persons during the hot season or while living in a warm climate cannot consume sufficient food to furnish the bodily requirements, and therefore lose protein and fat. During the winter months these losses are replaced [E. Ranke (3A)].

Atwater and Benedict (6) have often met with similar irregularities. The nitrogen excretion in one of their experiments, when the diet was a constant one, amounted to 17·2, 17·6, 14·2, 23·8, 20·3, 17·4, 17·2, 17·4 grammes. Psychical causes were presented to account for these differences. In this case, the anxiety felt by the individual about going into the respiration chamber occasioned a rise in protein metabolism. If the protein metabolism on the last day of an experiment be markedly influenced by some conditions lying quite outside the plan of the experiment, the result of the whole series may be seriously affected, and this will be all the more marked the shorter the series. After any experimental interference with a normal individual, or still more in the case of patients suffering from disease, it is essential that the investigation should be prolonged for a number of days.

(b) Variations in the Protein Intake.

(a) *Upper Limits of the Protein Intake.*

It is only the carnivora, not man, who can supply the energy requirements on a purely protein diet. In order, for example, to furnish the necessary 2,500 calories much more than 600 grammes protein would be required. Only those natural conditions will here be referred to when abnormally large quantities of protein are taken. In individuals who are in the habit of taking large quantities of meat in their diet without at the same time carrying out severe work, the daily protein metabolism rarely rises above 150 to 175 grammes. During the most severe muscular work, where the energy requirements are twice the normal, or even more, the necessary amount of food can still be satisfactorily taken, as investigations on bricklayers, Bavarian peasants, and athletes have shown [C. Voit (7)]. In such cases the diet need not be regarded as extravagant. In forced feeding, especially in cases of emaciation, the protein intake may be increased enormously. In Hirschlaff's case, a patient suffering from Graves' disease consumed during a period of forty-six days from 218 to 240 grammes protein daily. Lüthje was able to give 300 to 400 grammes protein daily in the form of some of the recent protein preparations which are more easily consumed.

As one may easily imagine, the diabetic patient is often able to consume very large quantities of meat. While the normal person is only able, much against his will, to consume 1½ kilogrammes of flesh for at most three days [J. Ranke, Rubner], the diabetic is often able to take such quantities for long periods. The most astonishing quantities may be taken when the patient strives to satisfy his appetite on a mixed diet. A diabetic patient of Fürbringer, weighing scarcely 50 kilogrammes, excreted during a period of five months, in addition to 600 to 800 grammes glucose, 40 to 60 grammes nitrogen daily in his urine ; and during a period of ten days, 800 to 1,100 grammes sugar and 60 to 76 grammes nitrogen. This corresponds to a metabolism of 400 to 500 grammes protein (7).[1]

(β) *Lower Limits of Protein Intake.*

Investigations dealing with this question arose from the discussion of Voit's standard dietary [F. Hirschfeld, G. Klemperer (8)]. Voit gave as a suitable diet for a strong man of 70 kilogrammes, doing a moderate amount of work, 118 grammes protein, 56 grammes fat, and 500 grammes carbohydrate—roughly, 3,000 calories per kilogramme body-weight. There were, therefore, 43·6 calories per kilo body-weight, or, allowing for losses by the fæces, etc., about 40 calories and 1·5 grammes absorbable protein. Since Hirschfeld and Klemperer, many workers have taken up this subject of the necessary protein minimum for the maintenance of body-weight. A large number of these investigations is given in the table on p. 300. It is not necessary at present to discuss these experiments in detail, as the adequacy of a small protein intake is now generally recognised. Only certain points will be here referred to.

In the case of all the experiments where the protein intake was small in amount the energy value of the diet was high, amounting in the experiments of Peschel, Kumagawa, Rumpf, Schumm, and Glaessner to over 50, in those of Klemperer up to 80 calories per kilogramme. Agreeing with the results obtained from other experiments, it is certain that a large supply of substances free from nitrogen allows the organism to easily accommodate itself to a low protein diet.

As strong confirmation of this, Klemperer's experiments may be quoted. In two individuals, nitrogen equilibrium was established rapidly within two or three days on the extraordinarily low protein intake of 5·28 grammes N. Still, the value of these experiments is much more theoretical than practical, owing to the excessive amount of food consumed (9).

F. Hirschfeld, C. Voit, Breisacher, Caspari and Glaessner were able to satisfy the body requirements with amounts of food the energy values of which were only slightly above the normal (45 to 50 calories per kilogramme).

Sivèn was the first to bring down the energy value of the diet to normal limits even when the protein intake was of the smallest. He brought it down to 42 calories per kilogramme, an intake which is by no means excessive. He only absorbed 6·25 grammes N = 39 grammes protein, or 0·66 gramme protein per kilogramme. The work of Neumann and Lapicque ranges itself alongside this, only in their case rather larger quantities of protein were taken (0·76 gramme to 1·1 grammes protein per kilogramme). In the case of the vegetarian school-girl examined by Albu, the intake of protein was 0·90 gramme per kilogramme, and the energy intake of the diet, which must be considered too low, was 1,400

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[1] During this time the patient showed a gain in weight amounting to many kilogrammes. The food intake must have amounted to between 4,000 and 7,000 calories.

Authors.	*Weight without Clothes.*	*Gross Intake.* Calories. Total.	Calories. Per Kg.	Nitrogen.	Protein.	Protein per Kg.	*Result.*	*Duration of Experiments in Days.*	*Remarks.*
				Gms.	Gms.	Gms.			
I. Klemperer (a)	64·0	5,020	80	5·28	33	0·5	After 3 days N equilibrium	8	—
Klemperer (b)	65·0	5,020	80	5·28	33	0·5	After 2 days N equilibrium	8	—
Caspari and Glaessner (a)	69·0	4,559	66	7·83	49	0·71	From the outset N retention	5	Vegetarian.
Caspari and Glaessner (b)	58·0	2,715	47	5·53	33	0·58	,, ,, ,,	5	Female vegetarian.
Rumpf and Schumm ..	63·4	3,432	54	11·8	74	1·15	,, ,, ,, (daily+0·9 gm.)	8	,, ,,
Kumagawa	48·8	2,478	52	8·75	55	1·14	N retained	9	Japanese diet.
Peschel	*circa* 75·0[1]	3,700	50	6·9	43	0·58	Only at the end N retained	8	—
II. C. Voit and Constantinidi	57·0	2,710	48	8·4	54	0·95	—	13	Vegetarian.
Hirschfeld	73·0	3,462	47	7·44	46	0·6	Only at the end N retained	8	—
Breisacher	57·1	2,866	45	10·8	67	1·19	N of fæces not estimated. Urine N remained 2 gm. below food N; certainly, therefore, N equilibrium was attained	30	—
III. Sivèn	59·0	2,477	42	6·26	39	0·66	N equilibrium	6	—
Lapicque (a)	73·0	3,027	41	8·8	55	0·76	N retained (0·5 per day)	8	—
Lapicque (b)	65·8	2,728	41	8·8	55	0·84	Small N losses	8	—
R. O. Neumann	66·2	2,659	40	12·2	76	1·1	Gain in N and body-weight	13[2]	—
Albu	37·5 (!)	1,400	37·3	5·46	34	0·9	Small gains in N	5	Female vegetarian; very small and thin.
Chittenden (a)	57·5	1,613	28	6·40	40	0·7	Daily+0·165 gm. N	6	—
Chittenden (b)	57·5	1,549	27	5·86	37	0·64	,, −0·07 ,,	6	—
See Note I.									

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[1] With clothing, Peschel's weight was 79·5 kilogrammes.

[2] For other similar experiments of Neumann, see p. 341.

Note I.—Collecting the results shown in the above table, the respective intakes were as follows:

0·5–·6 gramme protein per kilo .. Klemperer, Peschel, Caspari and Glaessner (*b*).
0·6–·7 ,, ,, ,, .. Hirschfield. Chitttenden (*b*), Sivèn.
0·7–·8 ,, ,, ,, .. Chittenden (*a*), Caspari and Glaessner (*a*), Lapicque (*a*).
0·8–·9 ,, ,, ,, .. Lapicque (*b*).
0·9–1·0 ,, ,, ,, .. Albu, Voit and Constantinidi.
1·1–1·2 grammes ,, ,, .. Neumann, Rumpf, and Schumm, Breisacher.

calories, or 37·3 per kilogramme. Chittenden[1] (9) has quite recently broken the record in a series of diet experiments upon himself. He was able, after some months' training, to maintain himself in N equilibrium on 37 to 40 grammes protein and 1,539 to 1,613 gross calories (= 0·64 gramme to 70 grammes protein and 27 to 28 calories per kilogramme).

All these experiments must be examined from another point of view—namely, from that of the individual who has to maintain N equilibrium on the daily dietary and for long periods. Most of the experiments are laboratory ones, and do not quite correspond to the conditions of daily life.

Breisacher and Neumann alone have drawn other conclusions from experiments lasting for thirty days or longer.

The experiments on vegetarians more nearly correspond to the ordinary conditions of daily life, but even they, as a matter of fact, merely give one an example of the effects of a one-sided dietary. Voit's "Euthalysianer" lost nitrogen in spite of an intake of 48 calories, and the persons who were examined by Albu[2] cannot be regarded as having been in a condition of good health on their low protein diet.

It was reserved for Chittenden to replace such laboratory experiments by a truly physiological one on a large scale, and to furnish complete evidence in favour of the view that a low protein intake is not only sufficient, but efficient, for the bodily requirements. He did not confine his experiments to those upon himself, but carried out similar ones upon twenty-five persons, the duration of these observations being also not limited to one or two weeks, but extending over five, six, nine months, and even longer. The plan of his investigations was, although simple, yet carried out on a very large scale, and the results which he has published in an important volume are of such extreme interest that it is advisable to give here some extracts from them.

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[1] *The Different Rate at which Individuals accustom Themselves to a Low Protein Diet.*—In men who have become accustomed to a diet rich in protein, a varying period elapses before their organism becomes adapted to the small intake, and the results of the diminution also vary in different persons. Thus, Sivèn (9) remained in equilibrium when he gradually diminished the N intake from 12·7 to 10·4, then to 8·7 and 6·3 grammes, the energy value of the diet amounting to 2,400 to 2,500 calories. (It was only when under the lowest ration that he lost temporarily some nitrogen.) Other individuals at once begin to lose weight when the protein is diminished in the diet. Most people in a short time come into a condition of nitrogenous equilibrium; others, however, in the short period usually devoted to these experiments never arrive at this condition. Caspari (9A) was not able in an experiment upon himself to arrive at a condition of N equilibrium within five days, when he diminished his protein intake from 83 grammes (13·3 N) to 63 grammes (10·1 N), although on a far richer diet (3,187 to 3,261 calories = 50 calories per kilogramme) than that of Sivèn. The loss of nitrogen showed no sign of diminution as the experiment proceeded. His view that the N minimum varies for different individuals might perhaps be better stated in this way. Some persons only arrive at N equilibrium after a longer period and after different losses of nitrogen, but this is at last attained by all and on the same diet.

Sivèn's special adaptability is shown from his second experiment, when very small quantities of protein were taken (10). In this case he lost proportionately very little protein, although he rapidly diminished the nitrogen in his food from 18 to 2·69 grammes. His loss was infinitely less than that of other investigators, where the diminution in the food was much less. He, however, was not able on this absolutely insufficient amount of protein to attain nitrogenous equilibrium.

[2] The person examined by Caspari was a vigorous gymnast, but he had during the experiment, unlike at other times, an excess of such substances in the diet as readily underwent oxidation (9).

Starting with the idea, gained from his personal experiments, that, in order to accustom the organism to a great diminution in the amount of the protein in the diet, it is necessary to bring about this decrease gradually, he carefully and slowly brought down the protein intake to a very low level in the case of all the individuals examined. This was done in practically all cases without eliminating animal food entirely from the dietary. As a rule, only certain directions as to the general character of the food were given, care being taken that there should be sufficient variety in the diet. No fixed rules were laid down as to the choice of particular articles of diet nor as to their quantities. Moderation was the sole essential condition. After a certain time, all who participated in the investigation began to look upon the restrictions as no longer unpleasant in nature, but rather the opposite. The energy intake, which was often calculated, scarcely ever rose above the bodily requirements, often, indeed, falling below them.

The first group examined comprised the scientific laboratory staff, a second one was made up of volunteers from the Army Medical Corps, these two doing a moderate amount of work; while a third division was made up of students engaged in active athletics, some of them being intercollegiate champions. The vigorous physiques of the men in this third class, as shown in Chittenden's book, must excite the admiration not only of the medical man, but also of the artist. These athletes continued their ordinary college studies during the time that they were in active training, and they thus required a decidedly higher energy intake than Groups I. and II. From their weight and the amount of work which they carried out, they corresponded at least to the average workman for whom Voit drew up his well-known diet table.

In the case of these twenty-six men, Chittenden estimated the nitrogen in the urine daily for five to nine months. He was satisfied, and rightly so, that the diet was a sufficient one if, after a temporary loss, the body-weight was maintained at its normal level for many months. They could then have lost neither protein nor fat. With few exceptions this was found to be the case.[1]

He regarded the urinary nitrogen as a gauge of the protein metabolism. The table on p. 303, compiled from Chittenden's figures, speaks for itself (10).

When the amount of nitrogen excreted in the fæces (1 to 2 gm.)[2] is added to the nitrogen excreted in the urine, one obtains for the N intake the following: Quantities of 56, 58, 63 to 67 grammes protein in the diet were found to be sufficient to keep all these men in nitrogenous equilibrium for many months. These quantities only represent 48 to 57 per cent. of Voit's standard.

[1] In the later months also the weights of some of the men varied. In fact, in the case of some of them the critical reader may well be in doubt as to whether nitrogenous equilibrium was really established. In the great majority, however, this was successfully attained. That apparent maintenance of the normal body-weight where a loss in the muscles is counterbalanced by a deposition of fat or an increase in storage of water, such as may occur in the experiments of short duration, could not possibly exist in Chittenden's series.

[2] Owing to the small amount of indigestible material in the diet, the daily quantity of fæces (and also their nitrogen percentage) was in some cases very small.

	Number.	Later Average Weight.	Alteration in Weight at Beginning.	Daily Nitrogen in Urine.	Daily Protein Metabolism (excluding Nitrogen of Fæces).	Nitrogen per Kg.	Protein per Kg.	Duration (Months).
		Kg.	Kg.					
I. Scientific laboratory workers	5	63·6 (57·5–70·0)	−2·9 (+1 *to* −7·05)	7·52 (5·7–9·0)	47	0·12	0·75	6–9
II. Medical Corps	13	61·5 (53–74)	−1·7 (+1·6 *to* −8·3)	7·9 (7·03–8·61)	49	0·13 (*circa*)	0·80	6
III. Athletes	8	70·0 (57·0–83)	−3·5 (0–9·2)	8·81 (7·47–11·41)	55	0·13 (*circa*)	0·79	5

Chittenden has confirmed the above results by exact nitrogen balances which he calculated in most of the persons investigated once, twice, or thrice during periods of five to seven days. It was only in the first and second groups, when the diet sank to 2,000 calories or less, and in the third, when it fell to 2,500 calories, that occasionally, although not always, a moderate loss of nitrogen was observed. The men, under a false impression of Chittenden's requirements, often at these times attemped to establish a record in the matter of diminished dietary. Most of these, however, engaged in the research preserved nitrogenous equilibrium even on the small amount of protein, and with a diet of very low caloric value. Also, during the months when the protein metabolism was calculated solely from the nitrogen output in the urine, the caloric value of the diet was never high. In Group II. it sank at times to 2,000 calories, never rising to 3,000.

Prior to the establishment of nitrogenous equilibrium at the new level most of the men sustained a larger or smaller loss in body-weight. This amounted to

An increase in	3 cases of	1 to 2	kilogrammes.	
" "	3 "	0 " 1	kilogramme.	
A decrease in	3 "	0 " 1	"	
" "	3 "	1 " 2	kilogrammes.	Average decrease in body-weight in 5 to 9 months 2·5 kilogrammes.
" "	5 "	2 " 3	"	
" "	2 "	3 " 4	"	
" "	3 "	4 " 5	"	
" "	1 case of	6·2	"	
" "	1 "	7·6	"	
" "	1 "	8·3	"	
" "	1 "	9·2	"	

The loss in weight was certainly due in part to protein waste,[1] but in these cases where it was large in amount a considerable proportion was due to loss in fat. The total intake of food was certainly at times insufficient. After the first half of the experiment the loss in body-weight, as a rule, ceased, and in the subsequent period both nitrogenous equilibrium and body-weight were maintained. In addition, the men gained in bodily strength and in what may be termed "elasticity." Many of the more highly educated men and the Army Medical Corps members became free from certain disorders which had previously given them trouble, and, as a result, they remained voluntarily and from conviction on the new diet. The thirteen men of the second group who engaged in gymnastic exercises for one and a half hours daily showed an increase of more than 100 per cent. in their dynamometric records. Even the athletes who had been previously in training showed an increase of 50 per cent. in muscular power. There was no sign of any deterioration in the composition of the blood nor in the reaction time for hearing, etc.[1]

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[1] If the total loss in body-weight were due to protein waste, which was certainly not the case, then on an average 80 grammes N were lost. The larger losses in body-weight —in four cases over 6 kilogrammes—were undoubtedly in the main due to loss of fat, as is distinctly shown from the description that is given by Chittenden of the individual cases. The first nine persons mentioned in the above table, owing to the very gradual diminution in the protein intake, have probably not lost any nitrogen, or, if they have done so at the outset, have soon overcome any such tendency.

Just as in Chittenden's book, so also in the writings of Ludovico Cornaro and Hufeland, the advantages that accrue from moderation in diet are emphasized (12). The doctrine of the sufficiency of small amounts of protein in the dietary has been expanded by Chittenden to a doctrine of the advantages to be gained by lowering the protein intake.

However, such a doctrine will not attract too many admirers, or at least will not bring them in as adherents, for the majority of men, even with the tempting prospect of a prolongation of life, or at least rejuvenation, prefer to enjoy the comforts of this life.

"... Ich kann mich nicht bequemen,
Das enge Leben steht mir gar nicht an."

The workman will still take a larger quantity of meat than the sedentary man. More protein is always taken during severe muscular work, and there must be a good reason for this. Voit gave the following explanation: Protein is not required directly for the muscular work, but the important muscle groups of the arms and legs which are required in the performance of ordinary work must obtain, in order to preserve the mechanism in good condition, a free supply of protein. Without this the musculature loses not only in mass but also in strength (13). This appears by no means incontrovertible. It is certainly true that, in passing to a diet poor in protein, the body loses at the outset nitrogen; but the total loss is small, and the functional capabilities may not be at all diminished. If the musculature is kept in good condition by continual exercise, even if the diet be lowered to less than two-thirds of Voit's standard, muscular strength and power of carrying out work may be actually increased. This is proved not only from observation of the conditions under which work is often carried out, but also definitely by Chittenden's experiments.[2]

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[1] J. Munk and Rosenheim observed severe disturbances in the dog when a diet poor in protein was given for a long period (11). These experiments have often been brought forward as strong evidence against diminishing greatly the quantity of protein in the dietary of man. They do not, however, affect the question. Even in dogs it does not appear as if it were the low nitrogen intake that produced the bad effects, but other conditions connected with the experiment—*e.g.*, they were given boiled, not raw, meat. Jägerroos has succeeded more recently in proving that dogs also may maintain their body-weight for months with a low protein intake (11).

[2] Three of the most distinguished of the athletes referred to by Chittenden may be mentioned. G. W. Anderson, "an all-round athlete,"; Bellis, "a gymnast acrobat in constant training"; and Stapelton, "a professional, a man of large body and great

Voit's standard is based less upon direct experiments dealing with the necessity of large protein intakes for the maintenance of musculature and power of doing work[1] than upon statistical grounds, such as the increasing amounts of protein taken by different individuals when the severity and amount of work which they are called upon to do increases. The explanation of this statement, which is absolutely correct so far as the above statistical evidence goes, is, however, in our opinion, a very simple one—so simple, in fact, that one hesitates before giving it, as it is so much of the nature of a commonplace.

A workman who finds a diet containing 80 to 90 grammes protein and of 2,300 caloric value sufficient for his resting requirements requires 700 to 800 more calories when doing a moderate amount of work, and 1,500 to 2,000 more calories for severe work. These extra requirements are not covered in the case of such a man by the addition of food-stuffs poor in or free from nitrogen, such as a scientific man or, for example, a chamois-hunter might add to his dietary. On the other hand, he simply takes more food of the same mixed composition as his resting diet, and therefore naturally increases his protein intake. Thus the fact that a diet of 3,000 calories includes 118 grammes protein, one of 4,000 calories 150 grammes protein or more, cannot be accounted for by any instinctive requirement on the part of the tissues, but rather by the usual composition of the dietary of man. To arrive at a diet rich in energizing material and poor in protein, one that may also offer variety and be sufficient for the bodily requirements, is the endeavour of the scientist. To the worker it is a matter of indifference, a question that does not come into consideration in the arrangement of his daily diet.

	Weight.	*Average N Excretion in Urine during 2 Months.*	*Metabolic Experiment (5 to 7 days).*					*Daily N Balance.*
			Intake.					
			Nitrogen.	Protein.	Protein per Kg.	Gross Calories (Total).	Gross Calories per Kg.	
	Kg.	Gm.						
Anderson ..	71	8·81	11·55	72	1·0	3,091	43·5	+1·71
Bellis ..	78	8·45	7·76	49	0·62	2,174	28·0	−2·09
Stapelton ..	75	9·00	11·47	72	0·97	2,809	37·5	+0·34

Bellis did not maintain his nitrogen equilibrium because he voluntarily reduced the amount of his food to an extent that proved harmful.

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strength." Their weights (without clothing), after the slight losses noticed at the outset, were respectively 71, 78, and 75 kilogrammes. In the above table their conditions during the last two months of the investigation are shown.

[1] Voit's experiments on dogs merely show that any increase in the amount of the protein of the organism (which may occur passively when a suitable diet is given) is frequently again lost on lowering the protein intake. But these results were derived from experiments on dogs in cages, and do not necessarily hold true for the animal at work.

An increase in the storage of protein in the body generally, and specially in the musculature, may, indeed, signify greater strength and capacity for work, but only when work and exercise are the causes which lead to the increased development. If the increase in musculatrue, etc., is merely passively brought about (diet), there is no increase in muscular power. In the same way, a moderate diminution in the cross-sectional area of muscles does not necessarily result in a loss of muscular power.

(γ) *The Average Efficient Intake of Protein.*

The high estimation in which the Munich scientist was held has been shown, perhaps, most clearly by the vigorous discussions which have taken place as to whether his standard of 118 grammes protein should be regarded as the normal one for an energetic man doing moderate work. Voit replied to those who suggested that the standard was too high a one that a smaller amount of protein was only sufficient in cases where the body-weight was below 70 kilogrammes, and where heavy work was avoided. However, this is certainly not true in many cases, especially in the case of Chittenden's students. Bearing in mind the difference in the requirements of different men, one must agree with J. Munk and R. O. Neumann that a protein intake of 100 grammes is sufficient even for a man doing heavy work (14).

It is certain that in cases where the diet is a full one a moderate diminution in the protein acts less harmfully than a free supply of protein with a caloric deficit in the dietary [Rechenberg, v. Noorden (15)]. In the latter case the body goes on losing fat continuously, and finally also protein; in the former the loss in protein does not go beyond a certain limit. The protein requirements may be reduced to a comparatively marked extent without harm; the caloric value of the diet, on the other hand, cannot be lowered, or only very slightly.

It is by no means permissible to explain any lowering of nutrition or of muscular strength, such as may occur in certain classes or among people living under unfavourable social conditions, as exclusively brought about by the smallness of the protein intake. Demuth found these deficiencies—the lowering in nutrition, etc.—in all cases when, even on a sufficient diet, the protein intake was brought down to 90 grammes (calculated for a body-weight of 70 kilogrammes), but an insufficient supply of protein was certainly not the sole cause of this. Of far greater importance was the whole social condition of the individuals—*e.g.*, the excessive work, insufficient recovery from fatigue, unsatisfactory state of the dwellings, maternal cares, etc. Economists are certainly going too far when they account for the physical and industrial inferiority of a people by the poverty of their diet in protein and the smallness of their meat consumption, as B. Niceforo has done in his comparison between the Italian and the English people (16).

On the other hand, Voit's normal standard has been of great value hygienically and socially in improving the diet. There is no doubt that a certain excess in the protein portion of the diet above that which is absolutely necessary will, in the case of individuals who have previously suffered from lack of food, do more good than harm. We must, although recognising the correctness of the results of Chittenden and his predecessors, at the same time bear in mind that a certain difference exists between their experimental conditions and those of daily life. Under the most favourable external conditions, a diet with low protein content could be arranged that would satisfy the requirements of the individuals who took a part in Chittenden's research. In ordinary life, however, a diet with so low a protein content, or even with a higher one, would, as a rule, prove unsuitable and insufficient.[1] Those who study the subject from the social and hygienic standpoint, instead of laying stress upon the necessity of a diet rich in protein, attempt rather to arrange a dietary for the masses that will not only be inexpensive, but also agreeable, and at the same time not monotonous in character.

They are just as far, however, from ranging themselves alongside Chittenden. It is true that Chittenden, from the results of his investigations, regards even what has been previously held to be a moderate protein diet as one that contains too high a percentage of protein. According to him, the capacity for work is increased, and a general feeling of fitness is more evident on the low protein diet than on the high one. One may scarcely call in question Chittenden's results, but the theoretical conclusions which he draws from them are after all rather too general and are scarcely warranted. That the organism may be injured by an overloading with the products of nitrogenous decomposition may be true in cases of disease, but is it true for the healthy individual? Are the carnivora less healthy than the herbivora because they consume a larger quantity of flesh?[2] The dangers resulting from the formation of toxines in the intestinal canal when large quantities of protein are taken seems scarcely to be founded on sufficiently strong evidence. Are we continually threatened by dangers of this kind, and are we actually always faced by two evils, the Scylla of the toxines and the Charybdis of the nitrogenous end-products?

Even if one grants that, in the normal decomposition of protein, bodies arise which may act injuriously, or may even be toxic in nature, still it is by no means certain that it is only the protein that furnishes such substances. We do not know enough concerning the intermediate products of fat and carbohydrate decomposition, but it is certain that many bodies do arise from them which, if they accumulate, may also act as poisons, or, at least, may produce disturbances in the organism. It is, perhaps, scarcely necessary to amplify this.

If Chittenden's men felt in much better condition during the experiment than prior to it, other causes than the small protein intake might have played a part—*e.g.*, the greater regularity of the life, the alteration in the meal-times, the total abstinence from alcohol, condiments, and such-like. If the 50 grammes sugar and 50 grammes fat that so often occur in the diet during these experiments were replaced by ¾ litre of milk, the result would probably be the same so far as concerned the general feeling of fitness, in spite of the extra 40 grammes of protein.

This is, above all, a return to simplicity, or, as it is often termed, "a return to nature." It has, in the hands of Chittenden and his pupils, been carried through with all the enthusiasm pertaining to a new cause. Vegetarianism, nature cures, etc., all have to thank this same tendency on the part of humanity for any real or apparent benefits derived from their use. These beneficial results are usually obtained in the case of individuals whose organs are not yet in a diseased condition.

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[1] Benedict (A. J. P., 1906, p. 409) traverses Chittenden's results, and concludes that permanent reductions of protein intake are decidedly disadvantageous and not without possible danger.

[2] The vegetarian, however, cannot range Chittenden on his side. It is true that a diminution of protein must be associated with a reduction of animal food, but Chittenden did not exclude meat, and his diet tables are absolutely different from those of the vegetarian and others of the same class.

It will be willingly granted by all that a greater simplicity of diet, and a reduction of the protein intake, may be of the greatest benefit, especially in the case of individuals who are in the habit of eating too much. In the case of those suffering from illness, the liver, kidneys, and perhaps, above all, the nervous system, may be injuriously affected by such a diet. It is possible that we may soon have a new system of dietetics in opposition to the forced feeding one. It will not be necessary, however, to carry out this new system to the extent that the scientific investigators did—in fact, it would not be advisable to do so.

(c) Alterations in Protein Metabolism due to Presence or Absence of Nitrogen-free Substances in the Diet.

(a) *Addition of Nitrogen-free Substances to the Diet.*

If an individual subsisting on a diet sufficient to maintain equilibrium, and with complete metabolism of the protein in the food, be given a larger amount of the nitrogen-free constituents, then a certain proportion of the nitrogen is retained in the body. This is apparently an exception to the statement previously made that the organism under all conditions seizes first of all the easily disposable protein. This may be explained, in part at least, by the Guldberg-Waage "law of mass-action"—namely, that the greater affinity of one substance for another may be overcome by the weaker affinity of a third body if it is only present in sufficiently large quantity to affect the reaction.

It is therefore necessary to give large quantities of carbohydrates or fats to spare small quantities of protein from being broken down in the setting free of the necessary energy for the different bodily processes. On a diet sufficient to maintain equilibrium not more than 15 per cent. of the previously metabolised protein can be spared by such additions as the above [C. Voit (17)].[1]

Two examples of Voit's experiments on the dog may be quoted (18):

Duration.	*Diet.*			*Metabolism of Meat.*
	Meat.	Fat.	Starch.	
	Gms.	Gms.	Gms.	
4 days	1,500	—	—	1,774
5 ,,	1,800	250	—	1,634
				Spared 140 meat = 30 grammes protein.
3 ,,	1,000	—	—	1,028
3 ,,	1,000	—	100–400	902
				Spared 126 meat = 27 grammes protein.

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[1] On the other hand, more than 15 per cent., even up to 50 per cent., of the total nitrogen excreted in a state of complete starvation may be spared by giving a free supply of carbohydrates (see following pages).

In none of Voit's numerous experiments did additions of 400 grammes carbohydrate or 200 to 300 grammes fat (with a caloric value of 1,600 to 1,800) spare more than 40 grammes protein from oxidation. It was only this amount which was spared through corresponding quantities of nitrogen-free bodies replacing it, the excess of the latter being stored as glycogen or fat, except that proportion which was used up from the increased activity of the digestive organs.

The conditions in the case of man are similar. In a case described by Deiters an addition of 200 grammes sugar caused a fall in the nitrogen excretion from 10·4 to 9 grammes, and in a second case from 8·7 to 7·5 grammes. Therefore only 7 to 8 grammes protein, equal to 13 to 14 per cent. of the previous amount which had undergone metabolism, were spared (19). (For a further discussion of this subject, see the parts dealing with overfeeding, especially as regards protein.)

(3) *Withdrawal of Nitrogen-free Substances from a Diet of Maintenance.*[1]

If large quantities of carbohydrate be withdrawn from a diet which had been found to be sufficient, then the breaking down of protein is increased. The organism passes into a condition of partial starvation, and seizes upon its own protein, in addition to the carbohydrate and fat stored in the tissues, in order that the bodily requirements may be satisfied.

The following table from Miura's work (20) will serve to illustrate this ;

Date.	*Intake.*				*Output of Nitrogen.*	*Balance of Nitrogen in Body.*
	Nitrogen.	Fat.	Carbohydrate.	Calories.		
November 26 to 28, 1891, average over 3 days	15·782	40·47	289·6	1,955	14·927	+0·862
November 30 ..	15·782	40·34	177·3	1,493	14·959	+0·830
December 1 ..	15·782	40·34	177·3	1,493	17·546	-1·757
„ 2 ..	15·782	40·34	177·3	1,493	18·452	-2·663
Average during the last 2 days ..	—	—	—	—	—	-2·210

In this case, as in others which will be immediately referred to, the nitrogen balance becomes worse from day to day. This is also seen in the experiments of Fritz Voit and B. Kayser. Now this is evidently due to the gradual disappearance of the stored up glycogen, until finally more and more of the protein is broken down to furnish the necessary energy (*cf.* also the conditions existing in complete starvation, p. 290) (20).

Just as addition of nitrogen-free food-stuffs will only spare a proportionately small amount of protein, so also a sudden diminution in the amount of those bodies in the diet only produces a slight increase in protein decomposition, by far the larger amount of the energy being obtained from the combustion of the tissue-fat and glycogen.

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[1] *I.e.*, a diet sufficient to maintain nitrogenous equilibrium.

	Nitrogen of the Food.	*Caloric Intake—*		*Diminution of Caloric Intake.*	*Caloric Deficit covered by—*	
		Before Withdrawal of Carbohydrates.	**After Withdrawal of Carbohydrates.**		**Tissue Protein.**	**Glycogen and Body Fat.**
				Per Cent.	Per Cent.	Per Cent.
Lusk, I. (21)	20·549	2,536	1,115	56	to 12·9	to 87·1
Lusk, II. (21)	9·23	2,182	668	70	„ 6·9	„ 93·1
Miura, I. (21)	7·28	1,820	1,361	25	„ 12·6	„ 87·4
Miura, II. (21) (*cf.* above)	15·782	1,955	1,495	29	„ 17·0	„ 83
Von Noorden	14·62	2,085	1,490	30	„ 8·9	„ 91·1

All these experiments were continued only for a few days. It may be supposed that, if the diminution in carbohydrate intake were persisted in for longer periods, the nitrogen losses, which at first increased in amount, would gradually become less, as is seen during starvation.

Addition or removal of small quantities of carbohydrates or fats from the diet has but little effect upon the protein metabolism. There are examples of this kind given in the experimental series (on dogs) published by the Munich physiologists (22). Von Noorden, from his own experience, brings forward evidence of the same kind in the case of men.

The effect of withdrawal of fat without the addition of any substitute to the diet has been shown by R. O. Neumann. On withdrawal of 78 grammes fat, corresponding to 725 calories, from a diet sufficient to maintain nitrogenous equilibrium, the nitrogen balance showed a total deficit of 7·5 grammes within four days. Within these four days the loss in nitrogen showed no sign in diminution. (For numerous similar experiments carried out on dogs, see C. Voit (23).)

(*d*) Comparison of Carbohydrates and Fats as Protein Sparers.

The action of carbohydrates and fats as sparers of protein, and the difference in the extent to which each may act, have been shown in various ways, all, however, being more or less similar in nature. The subject may be investigated in three ways. In the first place, one may study the effects of adding or withdrawing isodynamic quantities of fats or carbohydrates from a diet which has been given for a long time. Experiments of this kind have just been described. The diet from which these food substances have been withdrawn, or to which they have been added, as a rule, has been one which was previously sufficient to maintain the organism in equilibrium, although this is not absolutely necessary. In the second place, one may study the effects of giving equivalent quantities of these substances to the starving organism. Numerous experiments of this kind were carried out by the Munich school on dogs, but very few have been carried out on man (Landergren). If a comparison of the protein-sparing action of each of these substances (as shown by the above-mentioned two methods) be desired, it is essential that only such experiments should be compared as have been carried out about the same time and on the same animal, or on the same man. In the third place, a comparison between these two food-stuffs may be instituted by adopting the following procedure: (*a*) All the carbohydrate, or (*b*) a definite proportion, may be replaced by fat in a diet of maintenance, and the effect upon the nitrogen balance observed [(*a*) Kayser; (*b*) Tallquist, Helleson, Atwater, and Benedict (24)].

Whichever of these three methods one may choose to employ, the substitution of carbohydrates for fats always acts more favourably on the nitrogen balance than the substitution of fats for carbohydrates. This holds good even for carnivora, although they are not adapted by nature for the consumption of large quantities of carbohydrates. Voit, in fact, showed first of all in the dog the superiority of carbohydrates over fats as protein sparers. In a series of investigations immediately following one another (and these are of the greatest value) 100 to 400 grammes starch, when added to a meat diet (Method I.), lowered the protein metabolism to a greater extent than 100 to 250 grammes fat, although the caloric value of the latter is much greater than that of the former (25).

A good example of this may be selected from E. Voit and Korkounoff (25):

Intake.			*Nitrogen.*		
Protein.	Fat.	Carbohydrate.	Intake.	Output.	Balance.
31·2	15·3	268·6	5·11	5·11	−0
31·2	133·8	—	5·11	7·56	−2·45
31·2	0·8	—	5·11	9·57	−4·46

Perhaps the superiority of carbohydrates appears even more striking in the case of experiments dealing with human beings. In the case of an individual in nitrogen equilibrium, Kayser found that with a constant intake of nitrogen the replacement of all the carbohydrates of the diet by isodynamic quantities of fat was followed by a total loss of 9·2 grammes nitrogen within three days, and the loss increased from day to day, being on the first day 1·77, on the second 2·48, and on the third 4·98, while in the previous and in the subsequent periods 1 gramme of nitrogen was daily retained. The conditions are less unfavourable when only a portion of the carbohydrates is replaced by fats (Method 3*b*), as in Tallquist's experiment. In the case of a diet containing 466 grammes carbohydrate in addition to protein and fat, he replaced 216 grammes of the total 466 by 96 grammes fat, so that even on the so-called "fat days" 250 grammes starch were consumed. A loss in nitrogen under these conditions only occurred on the first two days, and then even only to a slight extent, while on the third day it had entirely disappeared. Helleson[1] obtained similar results—namely, moderate nitrogen losses—

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[1] In the experiments of Kayser, Tallquist, and Helleson (24) the body-weight decreased always to a remarkable extent during the period when the carbohydrate intake was diminished, water being given off. Kayser excreted on the "fat days" more water in the urine than was taken in the form of drink. Some years earlier Voit found that the same occurred in the dog. This, perhaps, is related to the exhaustion of the depôts containing glycogen (see section on Water).

in a method adopted by him for reducing obesity, and the same holds good for the experiments of Atwater and Benedict, where the protein-sparing action of carbohydrates and fats were studied in the case of individuals performing heavy work. In these researches also only 30 to 50 per cent. of the carbohydrates were replaced by fat. The nitrogen balance in the "fat series" was always 1 to 1½ grammes worse than in the "carbohydrate series" (24). (See section on Muscular Work and Metabolism.)

The superiority of the carbohydrates is especially well shown in nitrogen starvation (Method 2). In the lower animals the excretion of nitrogen in the urine may be markedly diminished by giving large quantities of different sugars [Hoppe-Seyler, Voit (26)]. This was especially noticeable in an experiment by Rubner (26), where nitrogen excretions (in starvation) of 1·92 and 1·82 grammes were brought down to 0·91 and 0·53 gramme[1] respectively after 83 to 120 grammes cane-sugar had been given. The breaking down of the tissue-protein in the starving dog is not decreased by giving fats—in fact, the nitrogen excretion often rises after giving large quantities of these bodies [C. Voit (27)]. This remarkable result has not yet been satisfactorily explained [Weintraud (28)].

Landergren has made a careful investigation of the conditions as they exist in man. The adult during the first days of complete starvation excreted 8 to 10 or 12 grammes (Landergren himself excreted 13·4 to 15·1 grammes nitrogen in the urine). When 700 grammes carbohydrate were given, the urinary nitrogen fell to 5, 4, or even 3 grammes. The nitrogenous excretion diminished to as great an extent when only 300 to 400 grammes carbohydrate were given along with very small quantities of protein and 100 to 150 grammes fat. When, instead of adding these to the diet, fat was exclusively given for four to five days in very large quantities (300 to 400 grammes), the loss of nitrogen was 3 to 5 grammes greater than in the carbohydrate experiments—that is to say, about 8 grammes nitrogen were excreted daily. In all his experiments, carried out in a variety of ways, the carbohydrates were found to exercise a much more favourable influence on the nitrogen balance than the fats (29).

Landergren does not believe that the difference between carbohydrates and fats as sparers of protein can be accounted for by their different physical and chemical properties, but gives rather the following possible explanation. If there are no disposable carbohydrates present, either in the food or in the storehouses of the body, then the organism must itself produce carbohydrate in order to satisfy its requirements. As, according to this investigator, a formation of sugar from protein may take place, but never one from fat (at least, under physiological conditions), then, in the absence of carbohydrate, a certain additional amount of protein must break down, in order to furnish the necessary carbohydrate requirements of the organism. Landergren estimates the absolute daily carbohydrate requirement of the adult at 40 to 50 grammes. In his opinion, 30 to 40 grammes of protein will be sufficient to furnish this amount if no pre-formed carbohydrates are present.

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[1] In this case, therefore, 50 to 70 per cent. of the protein previously metabolized was spared. The absolute quantities are naturally small.

This decomposition of protein for the purpose of furnishing sugar only, then, comes into question—and in this most will agree—if the carbohydrates be entirely excluded from the diet. It will not occur if the carbohydrates are only partially replaced by fats (*cf.* also the experiments of Kayser and Tallquist in the preceding pages).

It is impossible in this place to go more fully into this subject; the main points are, after all, easily comprehended. (For the significance of alcohol in protein metabolism, see Index.)

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4. Retention of Nitrogen in Forced Feeding.

(*a*) Methods and Results.
(*b*) Theoretical: Nitrogen, Egg-white, or Flesh, "Forced Feeding."
(*c*) The Value of Forced Feeding and the Duration of its Effects.

(*a*) METHODS AND RESULTS OF FORCED FEEDING.

There are certain exceptions to the rule that the organism strives to regulate the metabolism of protein according to the amounts presented to it, and hence tends to oxidize all the protein of the diet. If this were not so, then not only growth, but also any alteration in the composition of the body would be impossible. In youth there is a retention of nitrogenous material during growth of the body, which is usually regarded as synonymous with a protein or flesh retention. The same occurs at later periods of life in the enlargement of single organs—as, *e.g.*, the hypertrophy of the uterus in pregnancy or the muscles from exercise. An increase in the protoplasm is especially evident when the body is striving to recover its old condition after having suffered severe losses during starvation, or after acute infectious diseases.

In order to appreciate the nature of this condition, it is important to know whether the healthy organism which has passed the stage of growth is able passively to increase the amount of protein in the tissues. This question is of fundamental importance. It is necessary to determine the extent to which this is possible, and also what diet is most suitable to effect the greatest putting on of flesh. Here only the conditions as they exist in the healthy adult will be dealt with.[1] The question as to whether the increase of tissue protein during youth and in convalescence follows other laws than those which govern the retention in the adult will not be discussed here.

Conditions have already been referred to where at least small quantities of the protein of the food may be retained in the organism. Every addition of protein to a diet sufficient to maintain equilibrium produces a retention of nitrogen for some days, and the provision of an excess of nitrogen-free substances produces the same result. In the case of forced feeding, both of these conditions must be taken full advantage of in order to effect nitrogen retention.

Forced Feeding in Man.

The first experiment on the healthy individual, showing no sign of wasting, was carried out by Krug, a pupil of v. Noorden. In the first place, he brought himself into a condition of nitrogen equilibrium during a preparatory period of six days, the diet being a moderate one (2,590 calories = 44 calories per kilogramme). He then raised his intake 1,700 calories by adding carbohydrates and fats to his diet (the caloric value of the diet was now 4,300, or 71 calories per kilogramme). During this time he retained on an average 3·3 grammes nitrogen in the twenty-four hours, amounting to 49·5 grammes in the fifteen days experiment, and the retention at the close of the experiment was as great as at the beginning (1).

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[1] For the conditions existing in pregnancy, see Index; for those concerned with the periods of convalescence and growth, see v. Noorden's papers and the articles by Czerny and Steinitz in this text-book.

Bornstein carried out his investigation in another way. Starting with a diet sufficient to maintain equilibrium, he added protein alone to his diet, the addition amounting to 40 grammes. The result of a fourteen days' experiment was a retention of about 16 grammes nitrogen. Bloch carried out a similar but shorter investigation (1).

Owing to the dissimilarity of the additions to the diet, these series are scarcely comparable without further data. In order to arrive at a knowledge of the best possible diet containing an excess of protein, it is necessary to study the effects produced on the same person by adding different kinds of protein to his diet, and it is also essential that the experiments be of a prolonged nature. The most recent experiments of M. Dapper, jun.,[1] Lüthje and others (see later), do not bring forward sufficient evidence to fulfil the above requirements (2).

Forced Feeding in Animals.

As the investigations on men are so few in number, it is necessary to fall back on animal experiments, and, in doing so, one must bear in mind the differences in carnivora and herbivora. The laws which hold good for these cannot without further evidence be regarded as holding true for men.

It is impossible to give even to carnivora an extremely rich flesh diet, consisting exclusively of protein (Voit, Pflüger). Large quantities of nitrogen-free food substances require to be given in addition. In order to obtain the largest deposition of protein in the body, one must not give large quantities of protein either with or without fat, but proportionately larger amounts of fat than protein (C. Voit). Bischoff and Voit's dog, when given 500 grammes flesh and 250 grammes fat daily for thirty-three days (following on a diet poor in nitrogen), put on about the same amount of flesh in the first and last days of the investigation, namely, on an average, 56 grammes daily, or 1,792 grammes in all. When 1,800 grammes flesh, with the same quantity of fat as above, were given, the animal put on flesh rapidly during the first days of the experiment, but this only lasted five days, nitrogenous equilibrium then being maintained; and the total gain in flesh in seven days amounted to 854 grammes. Krug's experimental conditions and the results from his investigations on human beings are in agreement with those of Voit's (3).

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[1] Dapper, junr., added at first 80 grammes starch (in rice); then, in addition to this, 40 grammes plasmon to a diet which was certainly by no means an excessive one—viz., 2,930 gross calories, or 32·5 calories per kilogramme (weight, 90 kilogrammes). The gain in nitrogen during the rice period was 3·32 grammes; during the rice and plasmon period, 2·55 grammes less than the former. Dapper's deduction is perhaps the correct one—that a small amount of carbohydrate is a better protein-sparer than a relatively larger amount of protein (40 grammes plasmon), but it is by no means conclusively proved, as the plasmon was only given after N retention had been going on for a comparatively long period, and hence the conditions for further retention were unfavourable (see following table).

The conditions are different in herbivora. Here much less protein is put on when the usual food is taken than in the case of the carnivora on their natural diet.[1] Hence in the sheep, unlike in the dog, the addition of protein is the essential thing in protein forced feeding. But in this case, undoubtedly, there is a simultaneous increase in the food substances free from nitrogen.

Pfeiffer and Kalb kept two fully grown sheep on a diet both rich in nitrogen and of high caloric value, and found that they on an average put on 0·97 gramme nitrogen daily during an experiment lasting 100 days, quite apart from the nitrogen in the growing wool.[2] The two control animals on a diet of similarly high caloric value, but containing less protein, only put on nitrogen for a short time.

Even with a large increase in the protein alone, without any increase in the carbohydrate, the sheep continued to retain a considerable amount of nitrogen for many weeks [Pfeiffer and Henneberg[3] (4)].

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[1] It is often expressed thus: that the herbivora have not the same capacity as the carnivora for utilizing protein. This is, however, incorrect. In the sheep examined by Pfeiffer and Henneberg (see note 3), there was an excretion of *circa* 32 grammes N when 168 grammes protein were added to the food, while the normal excretion was 8 grammes N. These animals were therefore able to break down four times the amount of protein that they used up under ordinary conditions. It is true that the herbivora do not appear to possess the same capacity of metabolizing protein as the dog, but this is really not due to actual inability to do so, but rather to the fact that the alimentary canal of herbivora cannot absorb so much protein.

[2] At the beginning of the experiment about 1·1, at the middle about 0·7, and at the end of the series about 1·15 grammes.

[3] These experiments on sheep were carried out in such a thorough fashion, and the results which were obtained are so valuable, that a short résumé of them is called for, especially seeing that, except in literature dealing with agricultural questions, no sufficient notice of them has been taken.

Two fully-grown sheep in good condition received during two periods, each of three weeks' duration, 800 grammes meadow hay and 200 grammes barley groats as their ordinary food. In periods 1 and 7 this was given alone (the food being barely sufficient to maintain the body-weight). In periods 2, 3, and 4 they obtained increasing quantities of conglutin (70, 140, and 210 grammes), and in periods 5, 6, and 7 diminishing amounts of conglutin were given.

The experimental conditions were the same throughout the whole investigation. The amount of food given in periods 1 and 7, 2 and 6, and 3 and 5 were for each pair exactly the same. There was always a difference of 56 grammes protein between each period and the succeeding one. The results in both animals were practically the same, and so the average of the two is given. The N gain in the table refers to the total bodily gain minus that occurring in the growing wool.

Period.	*Duration in Periods of*	*Food.*	*N Balance for the Day.*	*N Balance for the Series.*	
1	21 days	Original diet alone	-0·44	- 9·2	—9·4
2	„	„ „ + 70 grammes conglutin ..	-0·01	- 0·2	
3	„	„ „ +140 „ „	+1·23	+25·8	+109·3
4	„	„ „ +210 „ „	+3·44	+72·2	
5	„	„ „ +152 „ dried and powdered flesh = 140 grammes conglutin	+0·54	+11·3	
6	„	Original diet + 76 grammes dried and powdered flesh = 70 grammes conglutin	-0·24	- 5·0	—23·5
7	„	Original diet alone	-0·88	-18·5	

It is unfortunate that the N balance is not given for each day separately, so that one cannot say whether at the close of the series 6 and 7 there was a tendency towards a

Bornstein's forced feeding experiments on men were similar, both in arrangement and results, to those of Pfeiffer and Henneberg.

An experiment of Max Dapper on himself is more difficult to compare. Dapper was able to obtain on a by no means excessive diet a distinct nitrogen retention, namely, 2·18 grammes per diem = 13·06 grammes protein in six days. This he raised to 3·32 grammes nitrogen retention daily (in twelve days 39·8 grammes) on adding 80 grammes starch to the diet. In a third series, when 80 grammes starch + 40 grammes plasmon were added to the original diet, he gained daily 2·55 grammes nitrogen, or 22·9 grammes in nine days.

Series.	*Duration (Days).*	*Diet.*	*Diet (N).*	*Diet (Cal.).*	*Nitrogen Balance.*	*Maxima and Minima of the N Gains (Gms.).*
1	6	Original diet	20·25	2,930	+2·18	+3·2 on 4th day; +1·5 on 6th day.
2	12	Original diet	20·09	3,250	+3·32	+4·75 on 2nd day; +4·65 on 12th day.
		+80 gms. starch	—	—	(+1·14 above Series 1)	+2·3 on 8th day.
3	9	Original diet	24·58	3,400	+2·55	+5·98 on 1st day.
		+80 gms. starch	—	—	(+0·39 above Series 1)	+4·73 on 2nd day.
		+40 gms. plasmon	—	—	(−0·77 below Series 2)	+0·5 on 6th day; +1·6 on 9th day.

In twenty-seven days 74 grammes nitrogen were retained. The losses in the sweat are not taken account of, and Dapper perspired freely. During the first days of the third and last series the greatest daily gain in nitrogen occurred; but subsequently the nitrogen retention, which in the first eighteen days showed variations, gradually diminished, this diminution continuing until the close of the experiment. The organism was, in the words of the writer, "almost saturated with nitrogen" from the preceding forced feeding. This is the reason why no further rise in nitrogen retention occurred on addition of protein to the diet, such as took place in Bornstein's experiment, carried out, however, under different conditions. In Dapper's second series, the addition of 80 grammes starch allowed 1·14 grammes nitrogen to be spared beyond that retained in Series 1. This was for a twelve days' experiment a very large retention (5). But the general conditions of the Rhinelander evidently were very favourable to the deposition of protein, and so his results can scarcely be regarded as holding good for other persons. The same diet produces on Cassius a different effect from that on Antonius.

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return to N equilibrium. With regard to the question as to the continuation of the gain in flesh on the return to the original diet, one is struck by the smallness of the losses in Series 6 and 7. This is all the more striking because, just as in Series 1 and 2, which were not preceded by a period when additional food was given, the animals were losing nitrogen; or, in other words, the diet was insufficient to maintain equilibrium. In Series 6 and 7 the increased loss was only 14 grammes greater than in Series 1 and 2.

Differences in the Individual Capacity for putting on Flesh.

As undoubtedly such differences do exist, it is necessary to carry out the experiments on numerous healthy persons. Only in this way can one discover which is the best kind of diet for this purpose, which leads to the greatest nitrogen retention, and which has the most beneficial effect upon the general condition.

If Bornstein's results show themselves to be generally applicable—namely, that small additions of protein to the diet gradually lead to small but regular protein accumulations—then a most important domain in dietetics has been opened up to the practitioner. A regular, if slow, increase in the protein content of the organism occurring without a simultaneous increase in fat deposition would be of incomparably greater benefit to individuals already supplied with a sufficiency of fat in the tissues than forced protein feeding rapidly carried out for short periods, for, in the latter case, it would be impossible to avoid a simultaneously occurring and useless deposition of fat.

On the other hand, if one desire to improve the diet of an individual suffering from wasting of the tissues of the body—and this, after all, is the more important case from the medical standpoint—then one must give large quantities of protein and also of nitrogen-free substances if the protein and fats in the tissues are to be increased in amount. Lüthje has shown what may be done in this direction, not only in the case of these persons, but also for those in good bodily condition. After giving an exceedingly rich diet (380 grammes protein and 6,000 calories), he obtained daily gains of nitrogen up to 10 to 20 grammes. This diet was given to two members of his clinique for a period of one to three weeks. It is true, however, that one seldom meets with an individual who can consume such a quantity of protein (5).

How do Different Protein Preparations act in this Matter of Forced Feeding?

Proteins containing phosphorus, especially casein, were at one time regarded as specially suitable. This belief was partly due to the fact that casein played such an important part in the infant's diet during the period of most active growth. Caspari found both in the dog and man a greater nitrogen retention after addition of casein to the diet than after a corresponding amount of flesh. Lüthje, however, found exactly the opposite, although his experimental conditions were precisely the same as those of Caspari (6).

From experiments where casein and other protein substances were not given in excess, but simply as substitutes (total or partial) for other albumins in a diet just sufficient for the requirements, the results which were obtained were also contradictory. Röhmann and members of his school found, as Zuntz had also done previously, that casein and vitellin given to dogs exerted a more favourable influence on the maintenance of nitrogenous equilibrium than other protein material. In Bloch's experiments on casein-feeding with men the results were on three occasions less favourable, and only in one more beneficial than when other proteins were given (6). The question is only of practical value for the invalid. Whether there are really any advantages to be derived from a casein dietary in such cases appears to the writer to be by no means proved—at least, from the contradictory evidence furnished by investigations on healthy individuals (6). With regard to the theories which have been held as to the advantages of one kind of protein dietary over another, see p. 65.

(For a discussion of the question of nitrogen retention during muscular work, see the section on Muscular Work and Metabolism.)

(*b*) THEORETICAL.

Overfeeding on Nitrogenous, Protein, or Meat Diet (Organized and Unorganized Protein).

In order to be in a position to discuss the question as to the form in which a protein or nitrogen gain to the organism may be attained, it is necessary to consider the relative importance of the different tissue proteins.

(*a*) *The Protein in the Organism (Organized and Unorganized).*

Ever since Voit's time a fruitful subject for discussion in the physiology of metabolism has been the difference between the protein of the cells, the elements in which the vital processes have their seat, and the protein which plays a more passive part in metabolism. Authors have given different names to these substances, according to the views which they held as to their significance. These are given in the following table (7):

I.	II.	
Organ protein.	Circulating protein	(Voit).
Organized „	Unorganized „	(Pflüger).
Tissue „	Reserve „	(Von Noorden).
	(Intracellular protein)	(Lüthje).
Living protein	Dead protein	(A. Fraenkel).
Stable „	Labile „	(Hofmeister).

Those terms included in the first table are practically all covered by organized, organ, or tissue protein, in so far as all imply the existence of active vital properties and a certain degree of permanence.

The terms in the second division can scarcely be grouped together in the same way.

The term with the most restricted meaning is that of "reserve protein." Its significance is merely this: that protein, just as glycogen, may be stored in the cell without becoming an integral part of its protoplasm (v. Noorden). About ten years previously Lüthje brought forward the same idea, and tried to support it from calculations based on the water balance (*cf.* pp. 329 and following). The term selected by him of "intracellular protein," (*Zelleinschlusseiweiss*) is recent. Voit's term, "circulating protein," signifies that it is nutritive material that is collectively easily decomposed. As Pflüger has said, however, it is impossible to localize the whole of this protein to the fluids of the body, and hence this term must be given up. It is advisable rather to start with the supposition that there is an organized and an unorganized variety [Pflüger]. By the former one signifies, in the main, the protein within the cells, by the latter that which is outside the cells and present in the circulating fluids—the blood, lymph, etc.—and also in the fluid that immediately surrounds the cells. Even this distinction is not free from difficulties whenever one analyzes it in detail. If the exchange takes place between the fluid bathing the cell, as Pflüger expresses it, or, in other words, if these by an exchange between the protein molecules of the cell contents and those of the surrounding fluid, then the same molecule which was unorganized outside the cell must be regarded as organized when it enters the cell. The terms "labile" and "stable" do not cover those of "unorganized" and "organized." They are merely general terms which signify the relative ease with which different proteins undergo decomposition in metabolism. It is true that the protein of the cell contents must be regarded on the whole as stable. The unorganized is, however, not synonymous with labile protein. It is certain that during metabolism it is in the main stable. For example, serum albumin, apart from its still unknown active functions, has certain more passive ones to perform as a constituent of the fluid which surrounds the blood and tissue cells. It must always be present in a certain proportion, and is, therefore, very largely stable in character. It is only a small proportion of that present in the fluids which undergoes decomposition—namely, that part which, being in excess, cannot be retained by the organism.[1] Inasmuch as the quantity of this easily decomposable labile protein which is present in the tissue fluids rapidly changes with the amount of the protein intake, the original classification given by Voit of this as circulating protein may be regarded as having the same significance. One must simply be careful not to limit its position to any fixed place—for example, labile protein may also be present within the cell.[2]

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[1] In this sense the term "instability" may be also applied to the inorganic constituents. Only one portion of the sodium chloride of the blood may be regarded as labile—namely, that which easily passes into the urine. The larger portion, as hunger experiments show, remains in the blood, in spite of the fact that the stable NaCl is diffusible, and is not bound at all firmly to the albuminates of the serum. Here, also, it is the excess which leaves the tissue and is excreted in the urine.

[2] A. Fraenkel's (7) classification of dead and living protoplasm has rightly never become established. The foundation of this classification is a hypothesis which is partly true—namely, that organized protein only then can break down when it, or, rather, perhaps, the protoplasm to which it belongs, is dead. It is, however, doubtful whether the protein decomposition in hunger is exclusively the expression of a spontaneous wearing out or death of cellular constituents. Is it not possible that the cell, in spite of its full vitality and perfect constitution, can still give off protein to supply the necessary functional requirements of the organism? The very marked sparing of nitrogen which can be brought about in the starving individual by giving large quantities of starch and sugar is strong evidence in support of the latter hypothesis. If, when 700 grammes starch are given to a man, only 3 to 5 grammes of nitrogen are excreted, while in complete starvation 10 grammes are lost, then it is reasonable to suppose that in the latter the 32 grammes protein that are broken down in excess of the former is not obtained from a store of dead protein destined solely for excretion, but, rather, that it is given off by the cell for a very definite purpose.

Fate of the Protein taken in the Daily Diet.

In order to understand what has now to be described, it is advisable to have a clear idea of what happens to the daily protein intake when the individual is not putting on flesh, but is simply in nitrogenous equilibrium. A part is used to supply the daily waste of the stable tissue protein. This is in part organized cell protein, as is very evident in the case of certain cells, such as epithelia of external or internal surfaces, red and white blood-corpuscles where the breaking down may be complete, or in many gland cells where the breaking down is partial. In addition, there is certainly also some stable protein which is not organized, and which breaks down.[1]

A certain proportion will also be stored in the organism replacing labile protein which has undergone oxidation. Only the nitrogen remainder, after subtraction of these two from the quantity of food absorbed, will give the amount that is excreted on the same day. Even if the nitrogen output be equal to the nitrogen intake, the daily urine does not exclusively contain the N taken up in the same twenty-four hours, but consists of a part of it, together with the nitrogen of broken-down tissue protein (stable and labile).

M. Gruber (9) held practically the same view. According to him, 80 per cent. of the nitrogen contained in the food was excreted in the urine of the first day, about 13 per cent. on the second, 5 per cent. on the third, and 2 per cent. on the fourth (these numbers were given by him as merely approximate). This hypothesis explains satisfactorily the nitrogen retention which occurs on feeding after a preceding hunger period, and also the greater nitrogen excretion on the first day after deprivation of food than on later ones. According to Gruber, on an intake of 100 grammes nitrogen in the food, there were excreted after a preceding period of starvation—

From the Food of the—	*On the Days during which Food was given.*					*On the Hunger Days.*			
	1st.	2nd.	3rd.	4th.	5th.	1st.	2nd.	3rd.	4th.
1st day (on which food was given) ..	80	13	5	2	—	—	—	—	—
2nd " " " ..	—	80	13	5	2	—	—	—	—
3rd " " " ..	—	—	80	13	5	2	—	—	—
4th " " " ..	—	—	—	80	13	5	2	—	—
5th " " " ..	—	—	—	—	80	13	5	2	—
	80	93	98	100	100	20	7	2	—

That portion (20 per cent.) of the protein of the food which did not undergo decomposition on the day of ingestion would remain in the body as labile protein until the time of its excretion. The above-mentioned statement deals, however, with more complicated processes, because it includes also the decomposition and then replacement of stable protein. In order to obtain a schematically clear picture of our statement, we only require to subtract from Gruber's 80 parts of the food nitrogen which underwent decomposition on the day of ingestion 30 parts for the replacement of stable tissue protein.

Scheme A (p. 323) would correspond to the conditions existing in a dog of average weight on a moderate protein intake (250 grammes of flesh along with fat), when only a small amount of labile protein remains in the body. Scheme B (p. 323) shows the N excretion on a large N intake. In this we take it for granted—a supposition that is, after all, not proved—that with a rich protein intake a distinctly larger quantity of food protein is not required for the replacement of the stable tissue protein than when the intake is smaller.

In Scheme B the amount of labile protein remaining in the body (=116 parts N) is much higher than in Scheme A (29 parts N), with a smaller protein intake. Corresponding to this, the rise and fall in the protein decomposition on the first " food " and on the first " hunger " days are much more rapid than in Scheme A.

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[1] After the observed minimal nitrogen loss in the healthy individual (3 to 5 grammes), we must, even under the most economical conditions on the part of the organism, give at least 20 to 30 grammes protein in order to replace the stable tissue protein. Under the normal conditions existing in the organism probably the amount will be much higher.

NEW SCHEME A.

f 100 Dcgm. Food Nitrogen of the 1st, 2nd, 3rd, etc., Days—	*There were excreted in the Urine—*											*There were stored as Stable Protein for the Replacement of the Organized Tissue Protein, and so not excreted for a Long Period.*
	On the Last Hunger Day.	On Food Day—					On Hunger Day—					
		1st.	2nd.	3rd.	4th.	5th.	1st.	2nd.	3rd.	4th.	5th.	
st food day ..	—	50	13	5	2	—	—	—	—	—	—	30
nd " " ..	—	—	50	13	5	2	—	—	—	—	—	30
rd " " ..	—	—	—	50	13	5	2	—	—	—	—	30
th " " ..	—	—	—	—	50	13	5	2	—	—	—	30
th " " ..	—	—	—	—	—	50	13	5	2	—	—	30
otal from food and labile protein	—	50	63	68	70	70	20	7	2	—	—	—
n addition from stable tissue protein	30	30	30	30	30	30	30	30	30	30	30	—
excretion in urine	30	80	93	98	100	100	50	37	32	30	30	—

NEW SCHEME B.

Of 300 Dcgm. Food Nitrogen of the 1st, 2nd, 3rd, etc., Food Days—	*There were excreted in the Urine—*											*There were stored as Stable Protein for the Replacement of the Organized Tissue Protein, and so not excreted for a Long Time.*
	On the Last Hunger Day.	On Food Day—					On Hunger Day—					
		1st.	2nd.	3rd.	4th.	5th.	1st.	2nd.	3rd.	4th.	5th.	
1st food day ..	—	190	52	20	8		—	—	—	—	—	30
2nd " " ..	—	—	190	52	20	8	—	—	—	—	—	30
3rd " " ..	—	—	—	190	52	20	8	—	—	—	—	30
4th " " ..	—	—	—	—	190	52	20	8	—	—	—	30
5th " " ..	—	—	—	—	—	190	52	20	8	—	—	30
Total from food of the same day and of the three preceding days (=labile protein)	—	190	242	262	270	270	80	28	8	—	—	—
To this there are added from the decomposition of tissue proteid which has been built up for a very long time from the food..	30	30	30	30	30	30	30	30	30	30	30	—
Nitrogen excretion in urine ..	30	220	272	292	300	300	110	58	38	30	30	—
		Period of rise in protein decomposition of the 1st flesh day.			Period of nitrogen equilibrium.		Period of the falling protein decomposition of the 1st hunger day.			Period of constant protein decomposition in hunger.		

(β) Destiny of the Surplus Nitrogen stored in the Body.

Physiological Form of the Surplus Nitrogen.

A nitrogen gain can be acquired by the body—

1. In the form of extractives (see following pages).
2. In the form of protein:
    - (*a*) As organized protein—true protein storage (see p. 327);
    - (*b* and *c*) As unorganized protein:
        - (*b*) As increase of the "labile protein";
        - (*c*) As reserve or intracellular protein, not organized, and not endowed with active protoplasmic properties.

There are two ways by which one may decide the question of the destiny of the surplus nitrogen:

1. The first method depends upon chemical examination of the tissues of the animal before and after the forced feeding, taking it for granted that the composition of an animal before the feeding is similar to that of a control animal. This plan has been seldom adopted. Kern and Wattenberg (8A) and other agricultural physiological chemists have made use of this procedure. Valuable information exists as to the important relation between the N and the water under forced feeding, but there are no well-planned investigations on the possible increase in extractives, etc., on the relation of the S and H_3PO_4, and many other points which would permit us to draw definite conclusions.

2. The second one depends upon the exact calculation of the N-balance along with the water and CO_2 (fat) balances, or also a sulphur or H_3PO_4 (and calcium) balance. These or similar combinations of these methods of calculation have been employed by most investigators as the groundwork of their investigations. All experiments up to the present dealing with the destiny of the surplus nitrogen begin with the attempt to determine whether in the stored substances (excluding the surplus fat) the relation between the nitrogen (protein) and water, or between the nitrogen and sulphur or phosphoric acid, is the same as in normal tissues. The method by which this is accomplished is shown in the following paragraphs:

1. *Retention of Non-Protein Nitrogen*

In the first place it must be regarded as highly improbable that a large amount of the nitrogen is stored in the form of non-protein substances. It is true that the amount of the non-protein nitrogen in every organ, and still more in the whole body, is by no means insignificant. Schöndorff found in the organs of a dog of 32 kilogrammes fed on a rich flesh diet (1,500 to 2,000 grammes) 40 grammes nitrogen in the form of extractives, and of this the half was not precipitable by phospho-tungstic acid.[1] But these extractives are also present in large quantities in the animal which has not been fed on a rich flesh diet (flesh extract). Only a small proportion of the nitrogen of the extractives is to be looked upon as end-products on their way to excretion (urea, ammonia, and other (?) substances). The quantity of these substances destined for excretion and stored within the body increases on forced feeding [as Schöndorff has shown for urea,[1] Salaskin for ammonia (p. 98)], since the increased formation of these substances is only counterbalanced by an increased excretion after a certain time has elapsed. The percentage amount of these bodies is somewhat augmented, but the absolute increase is comparatively small (8B).

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[1] This is by no means surprisingly large, because a dog of this size contains altogether about 800 grammes N (at the least 660 grammes). The extractive N amounts only to 5 to 6 per cent. of the total N. The muscle flesh of the herbivorous ox has, according to Frenzel and Schreuer (8B), who give the lowest numbers, 7·2 to 8·9 per cent. of the total N in the form of non-protein nitrogen.

It is certain, however, that the larger part of the actual extractives cannot be regarded as useless excreta or decomposition products. The constancy of the creatinin contents of the muscles must be borne in mind, and this, like the other extractives, must have a certain function. A marked rise or fall in the amount of these substances without an alteration and disturbance in the functions cannot be imagined. It has been shown that, on a rich meat diet, creatin does not remain in the organism, but is completely excreted within the twenty-four hours, although its derivative, creatinin, is soluble with difficulty [Gruber (9)]. After the discontinuance of a rich meat diet which had been given for several days, the excretion of creatinin fell at once on the first " hunger " day to the lowest point observed during starvation, while the total N excretion only fell to this extent after some days had elapsed. The extractives taken on the flesh diet are, therefore, certainly not stored on a diet containing a surplus of nitrogen. Neither has a storage of protein derivatives, such as albumoses, peptones, amino-acids, etc., been observed.[2] The storage of such a body as Pflüger's unknown nitrogenous substance is only a hypothesis, used as an argument by him in a discussion with the Munich school (9).

Gruber has further shown that the portion of the nitrogenous material stored on a surplus flesh diet of short duration which is again lost during the first days of starvation (corresponding to Voit's " circulating " and Hofmeister's " labile " protein) contains as much sulphur as the protein.[3] Therefore the nitrogenous substance which is retained in the body on the days when an excess diet is given, and which is easily broken down during starvation, is not a sulphur-free extractive, but apparently protein.[4]

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[1] The increase was only shown by Schöndorff for urea. He was able to separate in pure form urea from the muscles of his animal, while in the case of an animal fed on the usual diet this was impossible. Schöndorff, however, gives no comparable numbers for the total extractive N for an animal not subjected to forced feeding. A determination of the alterations in the extractive N in forced feeding is very much to be desired.

[2] Kern and Wattenberg describe an increase in the " soluble protein " on a surplus protein diet, but they were dealing with growing animals.

[3] The ratio between the urinary nitrogen and sulphur was normal. Gruber rightly estimated the total sulphur.

[4] It must be at once conceded that this conclusion, drawn from the relation of the sulphur (as also the similar one for phosphoric acid) is not absolutely proved; for it is at least possible that a sulphur-holding body such as taurin might be retained in the body as a cholalic acid compound at the same time that sulphur-free extractives are retained. It is precisely in the case of a rich flesh diet that an increased bile formation is observed, and thus the biliary sulphur, circulating in a large quantity between the intestine and the liver, is present in larger quantity than is required for digestion during the starvation period, and so could be excreted along with any nitrogen that had been retained without disturbing the ratio between the urinary sulphur and urinary nitrogen.

It may be taken for granted that the more stable part of the retained nitrogen which is not excreted during the first days of starvation is of the same nature (9).

In Rosemann's experiments on a medical man whose metabolism was apparently abnormal, and who had for a long period been taking iodide of potassium, the great variations in the N excretion (about 10 grammes N) on a regular diet were more probably due to a disturbed protein metabolism than to a retention of the end-products of nitrogenous metabolism. If the latter were the true explanation, as Rosemann believes, then this observation would be a unique one, as such a retention has not been described by any other writer. If the sulphur metabolism had been observed, a clear explanation might perhaps have been obtained (10).

There is still another reason that may be adduced against the hypothesis of a retention of extractives, and that is the behaviour of the phosphoric acid. If nitrogen is stored in the body, there is also a storage of a certain quantity of phosphoric acid. The parallelism between N and H_3PO_4, which was first observed by E. Bischoff, is most distinctly to be noted in cases where as simple a diet as possible has been given for long periods. In Bischoff's experiments on a dog kept on a flesh diet the ratio between the retained N and P was practically the same as in muscular tissue. There must therefore have been a retention of a substance containing phosphorus, and it must have been stored as flesh, and not as nitrogenous extractives free from phosphorus. In Sherman's investigations, which were carried out on men kept in the same way on a simple diet—namely, biscuits and milk—the results were similar to those of Bischoff (11).

Also, many of v. Noorden's school [Kaufmann and Mohr, Kaufmann, Dapper, jun.], and also Lüthje, Berger, and others, showed the existence of this direct connection between the N and phosphoric acid balances (12). It is, of course, known that phosphoric acid is not only stored in flesh, but also may be retained in large quantities in bone. A parallelism does not always exist between the N and P balances ; nitrogen may be lost while phosphorus is being stored, and *vice versa*.[1] In spite of this departure from parallelism, the close relationship existing between the nitrogen and the phosphoric acid may be regarded as strong evidence against a storage of extractives, and in favour of a true tissue increase or protein storage.

It is very improbable that a large proportion of a considerable nitrogenous retention is ever in the form of extractives. The main part is undoubtedly true protein storage. The question arises as to what happens to the surplus protein.

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[1] Read the discussion on the subject of intracellular protein and the critical remarks on phosphoric acid in the section on the Metabolism of the Mineral Salts.

2. *Retention of Protein.*

(*a*) *As Organized Protein* (*Flesh Storage*).

Is there a true retention on a surplus flesh diet ?

In order to be in a position to answer the question whether on such a diet protein is actually organized and deposited as flesh, it is best to start, as Pflüger (13) did, with investigations of long duration such as are carried out usually in the case of the stall-feeding of animals in agriculture. Such a prolonged retention of protein as occurs in these cases is always without hesitation regarded as resulting in true fattening (deposition of flesh). This signifies naturally not only an increase in the musculature, but also in the other tissues, glands, etc. A prolonged increase in the amount of protein stored in the tissues (amounting to about 33 per cent. of the amount at the beginning of the process), extending over many months, has been observed not only in pigs, but also in sheep and dogs. This cannot be anything else than a true flesh deposition. Pflüger calculated that there was a daily gain of 169 grammes flesh when pigs were kept on a fattening diet for four months. The ratio between the water and the fat-free solids remains the same in such an animal during the fattening process as before it, and this constitutes the strongest evidence in favour of a true flesh deposition. For every 21 to 22 grammes dried and fat-free muscle substance there are always 78 to 79 grammes water before as well as after the fattening process ; that is to say, the retained material shows the same ratio between protein and dried substance as in the original flesh, and so from the identity in composition we must regard the deposition as being one of flesh.

Pflüger rightly maintains that a retention of proteins to the extent above mentioned could not possibly take place in the tissue fluids. The serum of mammals contains for each 9 to 10 per cent. protein 90 to 89 per cent. water. If the stored protein were retained in the fluids, as there is no distinct increase in concentration of the serum, for every part of protein there must be a retention of at least 10 parts of water in the body. The increase in weight that would thus be brought about would far exceed that which has been observed (13).

An increase in flesh signifies, in the case of an animal that is no longer growing,[1] an increase in volume or a hypertrophy of the individual cells, and not an increase in their number. Generally speaking, in addition to the increase in organized protein, there is at the same time an increase in the unorganized protein of the circulating fluids, as an increase in the mass of cells which require nutriment must be accompanied by a corresponding increase in the nutritive fluid.

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[1] In the case of the fattened pigs the animals were apparently still growing, and hence Pflüger's argument is somewhat weakened. A true flesh deposition with similar results has, however, been definitely proved in the case of fully-grown sheep. Pfeiffer and Henneberg, and also Pfeiffer and Kalb, have, in contrast to Kern and Wattenberg, been able to effect a storage of fully 100 grammes N in the fully-grown sheep within 100 to 150 days. The fully-grown dog can be so fed that it puts on about 50 grammes N [Bischoff and Voit, etc. (13)]. Also a cat (weight at outset 3,530 grammes) put on 820 grammes within ten days on a flesh diet. Here the gain consisted mainly of "flesh."

It may be regarded as certain that even in the case of shorter series of experiments, just as in those of longer duration, a true flesh deposition may be attained when there is a large nitrogen retention. Here also the proof rests mainly on the fact that protein and water are retained in the body in the same proportion that they exist in flesh—*i.e.*, with 4 parts of water.[1]

One gramme N corresponds to 6·25 grammes protein and 29 to 30 grammes flesh. Pflüger calculates for his dog that, with a N retention of 46·1 grammes (= 288 grammes protein), there was a deposition of 1,397 grammes flesh along with 1,091 grammes fat in a nine-days series. The observed increase in weight (2,500 grammes) agrees almost completely with the calculated increase (2,488 grammes). Although such calculations in many cases agree, one must remember that for the satisfactory proof of their correctness an investigation of the uninterrupted and total CO_2 output and the water balance carried out for some days successively is not only advisable, but necessary.[2] One can only then state definitely how much of the increase in weight is due to fat and glycogen, and how much to protein and water.

It is certainly difficult to define the limit when the protein deposition no longer leads to an increase in the cell and tissue substance. Although in Bornstein's experiment (14), which extended over two weeks, there were each day small amounts of protein stored, one could not with certainty speak of a flesh retention with the small amounts that were retained, any agreement between the calculated and observed increase in weight being insufficient to permit a definite conclusion on this matter. But if one supposes tha tin Pfeiffer and Kalb's sheep (Note 1, p. 327) retention of N took place to the same extent as in Bornstein's shorter experiment—namely, a daily retention of 1 gramme maintained for 100 days—then one must regard the retention in Bornstein's case as possibly at least of the same nature as in the longer series (14).

(*b*) *Retention of Labile Protein.*

If, on the other hand, only a few grammes are stored within the body for some days, and if these be again lost within a short time, as frequently occurs, then one must not necessarily conclude that there has been a firm intracellular deposition.

It is probable that it circulates partly as "labile protein" in the fluids, and partly remains unorganized in the cells.

The quantity of labile protein, which is to be sought for in the fluids, varies with the protein intake, becoming practically zero after prolonged starvation. A sufficient diet leads to a certain physiological excess in protein, which varies within wide limits. A temporary increase in protein is possibly in the first place due to an increase in the labile protein. The protein therefore does not require to be organized.[1]

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[1] Another proof is given by the simultaneous retention of P_2O_5.

[2] Pfeiffer and Kalb have not, so far as can be made out from their description, estimated the CO_2 output on many successive days, but always simply during isolated periods of twenty-four hours.

In addition to the question of the retention of the surplus protein in the form of organized protein in the cells, and of unorganized in the fluids, there is also the possibility of its retention as reserve material in the cells.

(c) *Retention of Intracellular Protein* (*Unorganized*).

Lüthje (16) believes that a part of the surplus protein may be stored within the cell, just as fat is there retained without water, or glycogen with little water.[2] According to him, this is of the nature of an unorganized form of protein stored with the cell.[3] This would not be stable in the sense that the protoplasm of the cell is, but, on the other hand, it is not so easily decomposed as the ordinary labile protein of the body which undergoes decomposition within a few days. As will be subsequently shown, it may, at any rate, be preserved within the body for a prolonged period.

Lüthje, therefore, is opposed to Pflüger, in so far that he believes that the retention of surplus protein within the cell does not result in an increase in the amount of truly organized cell protein. Speck (16) holds exactly the same position. The most important element in Lüthje's line of argument is the experiment in which a disproportion is shown between the quantity of protein retained and the amount of water bound to it. He founds his views upon the differences between the calculated and the observed increase in weight. In his experiments the actual rise in the body-weight was less than the sum of the retained fat and the amount of flesh deposited as calculated in the usual way from the gain in nitrogen—a deficit in one case of about 2 kilogrammes, in another of even a larger amount. Therefore the surplus protein, or a part thereof, was not stored as flesh with 4 parts of water, but with a smaller quantity—that is to say, the deposition must have been in another form.

Similar differences in weight are to be noted in the investigations of Krug, L. Mohr and Kaufmann, Lüthje and Berger, Dapper, jun., and others, but objections of various kinds may be raised against all these calculations.

(1) In many of these investigations the estimations of the body-weight

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[1] The oxidation of these protein molecules, just as that of the fats and carbohydrates, cannot take place in the fluids outside the cells, but only after they have formed a chemical compound with the protoplasm. This, according to Pflüger, is a larger and more complex protein molecule (15A). In this sense of an addition of nutritive substances as side-chains to the principal chain of the large vital protein complex, an "organization" must precede every oxidation and combustion of the food-stuffs. If, however, we understand by organization a process by which the molecule taken up becomes an active constituent of the cellular protoplasm, able independently to carry out for long periods metabolic changes within the cell, we cannot speak of a true organization in a case where the added material takes the form of labile chains which easily undergo decomposition.

[2] Pflüger occasionally refers to the possibility of liver cells storing protein in the same way as fat and glycogen (16).

[3] V. Noorden's hypothesis of a reserve protein is practically the same as that of Lüthje, only at the time that he referred to it he did not base his supposition upon the water and protein retention. Our criticism of Lüthje's views refers especially to the water balance.

are unreliable. For example, it is remarkable that in many cases the weights are not given for the morning following the last experimental day.[1] (2) The calculation of the fat-consumption—in itself uncertain without the twenty-four hours' CO_2 estimations—is in all probability too low in these forced feeding experiments. It has not been reckoned for man how high the increased energy consumption rose in cases where there was such a colossal protein metabolism as in Lüthje's experiments. From the numbers obtained by Rubner and Magnus-Levy in animals (see p. 210) it must be very high. The calculated storage of fat would therefore appear too high. (3) It is also very probable that where the nitrogenous metabolism is so great the loss of nitrogen by the skin must be distinctly higher than on an ordinary diet, so that instead of a daily excretion of a few decigrammes, it may rise to a much higher level. In none of these experiments was the cutaneous excretion determined. In an investigation of fourteen days' duration, the loss by insensible perspiration might possibly amount to 10 to 14 grammes nitrogen. If this were so, then the gain in nitrogen, as well as that of fat, is reckoned above its true value. The actual water storage would therefore be greater than that calculated by the writers, and might perhaps, after all, be in the true proportion to the protein storage. (4) The variations in the water content of the body which occur under normal conditions are also to be remembered[2] (see the section on Water Metabolism).

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[1] In Lüthje's case the weights amounted to the following on the days mentioned:

Eighteenth.	*Nineteenth.*	*Twentieth.*	*Twenty-first.*
Kg.	Kg.	Kg.	Kg.
85·87	86·05	86·85	87·68

It was not estimated on the morning of the twenty-second, the close of the experiment. By equal progression it would have been about 0·6 to 0·7 kilogramme higher. Such a difference in a short investigation is, however, of great importance.

[2] Seeing that in Lüthje's first case 48 grammes nitrogen were given off in the period from October 18 to 27 (p. 28), and the weight during this time rose about 0·7 kilogramme or 1·2 kilogrammes, there were evidently great variations in the water as a result of the diet. (It is true that the result might be explained otherwise, namely, that in this case a part of the intracellular protein (48 grammes nitrogen) was lost, while another part was later organized as flesh by a subsequent retention of water).

There is a tendency in the case of many individuals who are in nitrogen and fat equilibrium to show variations in weight due to alterations in the amount of water in the body. In forced feeding this variability in the water content is often very pronounced, not only in individuals suffering from disease (see diabetes), but also in healthy persons. An example may be quoted: Dapper, jun., in three successive series, during which the caloric and nitrogen intake did not show excessive variations (see the table on p. 318), retained 39·8 and 22·9 grammes nitrogen. The variations in weight, on the other hand, amounted to −2 kilogrammes, +0·9 kilogramme, and +1·3 kilogrammes. Dapper explains the loss in weight in the first case, where there is a nitrogen gain, by a diminution in water resulting from a decrease in the consumption of fluid. In this he is certainly correct. When such water variations can take place in the organism of the normal individual, one can readily understand how uncertain all results are which refer any increase in weight to flesh deposition, fat storage, or gain in water, without having in the first place estimated the total output of nitrogen by all channels and without having carried out twenty-four hours' respiration experiments. In prolonged experiments the fallacy resulting from the variability in the water content is much less serious, as one has not to calculate for more than a 2 kilogrammes "physiological water difference." In the total balance of a long series it will only amount to a small weight. But even in the case of absolutely regular ordinary dietetic and forced feeding experiments a plus or minus of 1 to 2 kilogrammes in the water content must always be considered in calculating the water balance, and one must not refer such a difference to a storage of water-free protein without sufficient evidence.

One must therefore keep in view the possibility of a storage of intracellular protein in forced feeding, but it has certainly not been proved up to the present that large quantities of surplus protein can be retained in this form.[1]

Long before Lüthje, T. Pfeiffer and Henneberg (18), in 1890, found a disproportion between the observed and calculated increase in weight on a surplus protein diet, and expressly stated that in their experiment protein was laid down in the tissues with a smaller amount of water than is present in flesh.[2] Their evidence is much stronger than that of more recent writers, as they carried out numerous respiration experiments of twenty-four hours' duration on the sheep — that is to say, the fat metabolism was directly estimated. They also paid attention to the gain in nitrogen by the wool. But one may also in this case raise the objection that the CO_2 excretion and the fat consumption might be higher in the stall than when measured in the respiration chamber. The fat storage would then be calculated as too high and the gain in water too low. For the CO_2 excretion was only estimated on isolated days, and during the longest period of the investigation, which lasted for many months, the animals were kept in the sheep-fold.

The relation of the phosphoric acid has also been considered as a means of deciding the question of intracellular protein. Dapper, jun., and also Lüthje and Berger, have not observed the phosphoric acid storage which has been usually observed in such cases of forced feeding, and have therefore concluded that the storage is not in the form of tissue, but as reserve or intracellular protein. The latter is supposed, in contrast to tissue protein, to be either free from phosphorus or poor in that element. But a gain or loss in phosphorus may be due to various conditions—*e.g.*, a storage of inorganic P_2O_5 in the soft parts and bones, or of organic phosphorus in nucleo-proteins and lecithins. Owing to the difficulty of apportioning the phosphorus, any conclusion drawn as to the nature of the stored protein from the amount of phosphorus which has been retained must be regarded as based on insufficient evidence (see the section on Metabolism of Inorganic Salts under the heading Phosphoric Acid) (19).

Two methods have been adopted by recent workers in order to gain an insight into the question of the reserve or intracellular protein—namely, by making a quantitative comparison between the N and the H_2O balance, and between the N and P_2O_5. If the theory (which still requires to be proved) is really correct, then both these methods must furnish the same result. In the exact sciences it is absolutely necessary, in order to prove the correctness of a theory based on the results of calculations obtained by the employment of two methods, that the results so arrived at should be in complete agreement. In biology, however, it is impossible to make such a rigid regulation, but at least an approximate agreement is required. After a critical analysis of the investigation on the subject of intracellular protein, it is impossible to find such a conformity. This must be emphasized, although at the same time one is sufficiently cognizant of the care which the writers have shown in carrying out their work.

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[1] Lüthje reckons for one case 206 grammes of intracellular protein (=33 grammes nitrogen). For a criticism of this case, see pp. 332-333.

[2] Svenson has also shown a disproportion in the case of a patient convalescent from typhoid. In this case, as he himself points out, it is doubtless due to variations in the water percentage of the tissues (18).

A specially striking example may be taken from Lüthje's and Berger's experiments (19A)—namely, the third experiment on p. 292 of their work. The amount of the intracellular protein is calculated from the phosphorus balance, and, in addition, the variations in weight are stated. A patient who had passed the earlier stages of convalescence after typhoid fever received in seven days, on an average, 54·6 grammes N, approximately 4,500 calories. In this time he gained 79·9 grammes N, which, from the ordinary method of calculation, would represent 2,349 grammes of flesh. The observed increase in weight amounted to 0·9 kilogramme.[1] From the proportions of the CaO, P_2O_5, and N retention, Lüthje calculates that 47 grammes N could have been deposited as flesh, but, on the other hand, that 33 grammes (= 206 grammes protein) were not united with phosphoric acid.

Such a retention in the body as 206 grammes of intracellular protein within seven days is sufficiently great to excite suspicion. But even putting this aside, there still remains a great disproportion between the observed increase in weight and that reckoned from Lüthje's own figures. Forty-seven grammes N correspond approximately to 1,400 grammes flesh, and to this must be added 206 grammes intracellular protein (the water necessarily taken up by this protein is not considered). The patient must, in addition, have put on some fat—at the lowest valuation[2] probably 100 grammes daily, or 700 grammes in the seven days. There must therefore have been deposited 1,400 + 200 + 700 grammes = 2,300 grammes. Now, the actual observed increase in weight was only 900 grammes, so that there is a deficit of 1,400 grammes.

If the calculation in this case, instead of being based upon the phosphoric acid, had been founded on the increase in weight, then the figures obtained according to Lüthje's old scheme would have been—

79·9 grammes nitrogen = 499 grammes protein
499 grammes protein = (100 × 5) flesh + 399 grammes dried intracellular protein
= 500 grammes flesh + 399 grammes dried intracellular protein
= 900 grammes increase on weight.

In this calculation the intracellular protein is regarded as water-free, and no reference is paid to any possible fat deposition. Also, in this case we are met with differences in weight which are not to be explained

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[1] In this case also the weight on the morning after the close of the experiment is not given.

[2] The daily quantity of dried fæces (64 grammes) contained 3·4 grammes nitrogen = 20 grammes protein, and in addition 12·4 grammes CaO + P_2O_5, and therefore, at the most, 32 grammes fat. The energy loss by this channel, therefore, amounted to 380 calories at most; 70 grammes protein were daily retained. The energy metabolism would certainly not be reckoned too high at 50 calories per kilogramme. The calculation gives the following figures:

Intake	4,500	calories	
Loss in fæces (calculated high) ..	380	,,	
Metabolism	58 × 50 = 2,900	,,	
Retained in 70 grammes protein ..	= 280	,,	
Remainder of calories deposited as fat	= 940	,,	= 100 grammes fat.

even on the widest interpretation of the theory of water-free intracellular protein. We come back again, if analytical errors are absent, to the view that there is a loss of water from all the tissues of the organism. It is impossible to refrain from expressing the opinion that many of these experiments on forced feeding show somewhere or other a gap in the evidence which the investigators seem to have overlooked.

The solution of this problem might be more easily attained by American workers,[1] as they not only have better laboratory equipment than the workers of other nationalities, but they are also more favourably situated in the matter of skilled assistance. In order to finally settle this question of intracellular protein, it is only necessary, as has been often done, to accurately determine the nitrogenous metabolism and the phosphorus and sulphur balances during uninterrupted series of forced feeding experiments for periods of eight days' duration. It would also be of advantage to estimate the other salts in the food and in the excretions. If the American scientists also calculated the amount of the actual protein and extractive N in the diet, and if they also estimated the oxygen intake, there would be a sufficiency of data to come to a definite conclusion. There would be a number of comparable figures furnishing the same result and controlling one another.

If the question be answered by such experiments as above described, in the way that Lüthje has imagined, then that theory which was formulated anew by him must be reckoned with. That it is a possible theory there can be no doubt, but it has not yet been proved. From investigations of this nature others will arise, and then we shall be in a position to state more accurately the conditions existing in the metabolism of forced feeding.

(γ) The Value and Permanence of the Effects produced by Forced Feeding.

In many cases a gain in nitrogen after forced feeding signifies a gain in flesh. This appears to be the conclusion which may be reasonably drawn from the above-mentioned researches.

But a new question links itself on to this conclusionI : s that protein which is taken up by the cells in forced feeding, and which increases their mass, really in the higher sense organized as is usually supposed ? Apart from the cell nucleus, the functions of which are at least partly understood, we do not know to what part of the cell protoplasm the so-called vital properties of the cell belong. Must we allocate the so-called organization and vital properties to the cellular spongioplasm,[2] or to the fluid constituents which occupy the interstices of the former—the paraplasm ? It is possible that the latter furnishes—at least, in part—the nutritive material for the true protoplasm,[3] and it is probable that its active functions are much less pronounced than those of the protoplasm. [Schäfer and others believe that it is the hyaloplasm which is the active factor in the protrusion of processes, the movements of cilia, muscles, etc.]

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[1] " Amerika, du hast es besser,
Als unser Kontinent, der alte."

[2] Previously this was regarded as fibrillar in arrangement; now it is more usually described as foam-like or honey-combed.

[3] For example, it is doubtful whether the hæmoglobin of the red blood-corpuscles is organized, and whether it may actively set up chemical processes other than those associated with it as the carrier of oxygen.

Pflüger (20) suggests the possibility of the fluid occupying the meshes of the network having its site defined by the active forces of the spongioplasm.

If with the putting on of flesh during long periods of forced feeding the proper ratio of protoplasm and paraplasm (that is, between higher and lower organized protein) is maintained, then we may refer to the increase as being truly of the nature of an "organization." On the other hand, it is possible that during shorter periods of forced feeding the paraplasm may show a greater increase than the protoplasm.[1] In this case an organization in the higher sense would not have occurred. Perhaps, as the cells are called upon to do a greater amount of work, they take up more nutritive material and transform it into organized matter. "In the organized cell substance there are without doubt different forms of organized protein molecules" (*Pflüger's Archiv*, liv, 419).

It is unneccessary to follow this subject further. Only when our knowledge of the structure of the cell and its functions has become much more exact than it is at present, may we expect to be in a position to solve these problems. When we know the constitution, quantity, distribution and significance of the different proteins in the various cells and organs of the body, then, and only then, shall we be in a position to discuss satisfactorily the questions as to organized and unorganized, labile and stable, reserve protein, etc.

At present we can only examine the question of the organization of retained protein from the standpoint of the increase in usefulness on the part of the organism. From the consideration of the following two questions this subject will be made clearer :

1. Does a diet of forced feeding result in an increase in the functional activity of the organism ?

2. On the return to the old diet after a course of forced feeding, does the organism firmly retain the protein which it has gained, or is this protein soon lost ?

1. In the case of the debilitated organism which has once more been brought up to its normal condition, both these questions may be answered in the affirmative. They are also true for the healthy individual in many cases—*e.g.*, when the organism with its hypertrophied musculature is kept in sufficient exercise by carrying out permanently a larger amount of work than previously. But it is scarcely imaginable that an increase in the mass of the protoplasm above the normal amount existing in the

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[1] This view is not identical with those of Lüthje on intracellular protein. A one-sided increase in the paraplasm, absolute or relative to the protoplasm, is associated with a corresponding addition of water, while Lüthje distinctly states that this does not occur in the case of his intracellular protein. Lüthje's intracellular protein is exclusively reserve material, and remains until required quite outside metabolic activity. Up to that moment it remains entirely passive. This does not hold good for any excess of protein in the paraplasm leading to an increase in its mass. Only in the matter of the minor degree of stability have these two types of protein anything in common.

organism—and without doubt each individual has such an average normal quantity—expresses a higher standard of health and vitality.[1] There is nothing beyond the standard of good health.

Every unprejudiced person, and every medical man not too deeply immersed in questions concerning nitrogenous balances, can cite many examples of increased muscular strength without any distinct alteration in body-weight or increase in musculature. To the mountain-climber, who is drawn year after year to the snow-clad heights, there comes sufficient reward even in the matter of health, in spite, perhaps, of fall in weight and a certain loss of protein. Anyone desirous of obtaining exact data on this subject would find it of advantage to peruse Chittenden's work (*cf.* p. 301 *et seq.*).

But the importance of an excessive protein dietary in the case of those who are suffering from general weakness, or who are debilitated for any reason, seems to be somewhat exaggerated at the present day. It cannot, however, be denied that such a dietary is often productive of good results.

But it appears as if we were going too far in regarding such a dietary as one of the most important therapeutic agents in the treatment of debility. Such a conclusion is not sufficiently well founded. To say that such a beneficial effect is one to be expected, and that the treatment is based upon sure experimental data, is to go beyond the evidence at our disposal. It is perhaps of some advantage to express this heretical opinion, but it is scarcely necessary in this place to discuss the matter further.

2. A permanent retention of the surplus protein has often been doubted; in fact, the opinion is often expressed that, on a return to the usual diet, the excess in the tissues is again lost. Clinical experience often favours this latter view.

Voit's authority may be quoted in support of it, as he held that any rise in the protein retention led to an increase in the metabolism. In order, therefore, permanently to keep up the amount of protein in the tissues at the high level, it is essential to permanently increase the intake of protein. Pflüger and G. Rosenfeld also favour this idea (21).

In the dog the increased amount of flesh that is put on during such a surplus diet is frequently lost on return to the normal food. The experiments of Voit were, however, not of sufficiently long duration to settle this question conclusively. The excellent investigations of

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[1] Pflüger, it is true, holds another opinion. He regarded every increase in protein metabolism as of advantage to the organism. Even if the amount of the protein intake in carnivora raises metabolism to a far greater height than is necessary, still, although the process appears an extravagant one, there is associated with the increased metabolism a more fully developed functional capacity, which renders the organism more resistant to any toxic influence (*Pflüger's Archiv*, liv, 319). Every addition of protein to the diet increases metabolism and the functional capacity of the individual. Every diminution in the daily protein intake decreases metabolism and functional capacity even when fats and carbohydrates of the same caloric value are given in place of the protein which has been removed from the food (*Pflüger's Archiv*, lxxvii, 481, 482). Pflüger brings forward the view, one which has been by no means proved, that the beneficial effects produced by an increased protein intake have in omnivora a definite maximum (*Pflüger's Archiv*, lxxvii, 482).

Pfeiffer and Henneberg on fully-grown sheep are conclusive, although their results are expressed in another form (22).

In the three intermediate series (3, 4, 5) of their extensive investigation the animal put on 109·4 grammes nitrogen in nine weeks exclusive of the nitrogen essential for the growth of the wool, the amount of nitrogen in the body being raised probably in each case 10 per cent. In the following six weeks (periods 6 and 7), on return to the food of periods 2 and 1, they only lost 23·5 grammes, or, calculating by another and more correct method, 14 grammes. The nitrogen balance of the individual days is unfortunately not given, so that it is doubtful whether the nitrogen losses continued after the conclusion of period 7. However, the larger proportion of the gain in protein appears to be retained, although the energy and nitrogen intake in the latter period was barely sufficient.

It is, therefore, not permissible to state as a general rule that the gain on a surplus diet is unstable—an opinion that is frequently expressed.

In similar experiments on man there are, as a rule, no calculations of the nitrogen balance on return to the normal diet.

Lüthje alone gives some such examples. One of the convalescents from typhoid examined by him showed, during a period of five weeks, a retention of 210 grammes nitrogen. In the following period of ten days he lost altogether 48 grammes nitrogen,[1] although on a protein and energy intake that would have maintained equilibrium had there not been a preceding period of forced feeding—that is to say, the 48 grammes represented a retention which constituted no permanent gain to the organism. These losses are proportionately high for such a case, namely, one dealing with a convalescent who, one should imagine, would tend to retain more firmly any gain in body-weight. The losses were smaller in the case of a second female patient who retained 147 grammes nitrogen during a period of ten days. In a subsequent period of nine days of complete starvation she lost only 70 grammes (?) nitrogen—not more, therefore, but actually less, than would be expected to occur in the febrile condition without the preceding period of forced feeding (23).

Lüthje and Berger gave two further series (23). Berger himself retained 32 grammes nitrogen during a seven-days' period of forced feeding on a daily intake of 25 to 40 grammes nitrogen and 2,700 to 3,300 calories. The nitrogen losses from the excessive perspiration in this case were not considered. This nitrogen gain was maintained during a succeeding period of five days, when a diet approximately sufficient to cover the body requirements was taken. A patient in the clinic retained 67·7 grammes nitrogen in ten days on a diet containing 52 to 58·6 grammes nitrogen and 3,300 to 3,550 calories. On return to the normal diet of 20 to 22 grammes nitrogen and 2,088 calories, 33·9 grammes nitrogen were lost in ten days. The nitrogen deficit was no longer noticeable after the first six days; in fact, during the last four days a slight nitrogen retention was observed. The permanent gain amounted to 33·8 grammes.[1]

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[1] On further prolongation of the experiment undoubtedly quantities of protein would have continued breaking down, as the nitrogen losses in the last five days of the experiment did not diminish.

Therefore in man also it is possible to obtain a retention of nitrogen which will be preserved by the organism for some time at least. Still, one cannot regard this as constant, simply because there are no experiments showing the opposite effect in man. Experiments of Tabora (23) might be quoted, although they were carried out for other purposes, but their results can only be used with caution in the discussion of the question of forced feeding and its effects. In a preceding period Tabora kept his patient on a milk diet not quite sufficient for the body requirements, then for six to nine days he added daily 120 to 200 grammes plasmon to the above dietary, and concluded by again giving the milk diet for three days. In half of the cases the gain in nitrogen which occurred during the forced feeding disappeared during the short concluding period of three days. Also, even in those cases where a surplus remained, the nitrogen balance in the final period was, in 60 per cent. of the cases, 3 to 9 grammes less than that of the first period, although in both cases approximately the same amount of nitrogen was taken in, and the diet was of the same caloric value, both being rather below the body requirements.

Doubtless in any subsequent experiments on healthy individuals the results will not be uniform. If a forced-feeding experiment were carried out on a person who tended to put on flesh—for example, in an individual whose weight increased from 78 to 99 kilogrammes in thirteen years—one would expect that a permanent protein retention might easily be attained; scarcely, however, in the case of a thin but muscular man whose weight remained constant for twenty years.[2] The results will depend, just as in the experiments on animals, on the individual's capability of undergoing muscular or other tissue development, and this varies with the race as well as with the individual.

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5. *Cf.* Nr. 1 und 2.

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[1] If the nitrogen losses by the skin were reckoned, the nitrogen gain during the period of forced feeding would be smaller, and the nitrogen loss in the subsequent period greater, than the above-mentioned numbers express.

[2] Both examples correspond to actual cases.

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5. Protein Metabolism in Underfeeding.

(a) *The Amount of the Protein Loss under Different Conditions.*

Underfeeding is frequently met with in daily life, either in cases where, the amount of work performed remaining constant, the quantity of food is diminished from some external cause, or some internal one, such as loss of appetite. It may also occur when the diet is normal but the amount of work is excessive. The former case will be considered first.[1]

One form of it has been already discussed, namely, too small a supply of protein in a diet otherwise sufficient (p. 299). Underfeeding in ordinary life usually occurs from an insufficiency of nitrogen-free substances, usually, it is true, associated with a diminution in protein.

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[1] For the requirements of an individual doing heavy work, see the section on Muscular Work and Energy Metabolism.

Such a condition results in a disappearance not only of the glycogen, fat, and the unstable protein of the body, but also of the intracellular protein. The results are similar to those observed in starvation, but they do not occur so rapidly.

Without altering the amount of protein in the dietary, and when this in itself is sufficient for the requirements, a removal of the carbohydrates or fats produced marked protein losses (p. 308). They will undoubtedly become even greater when the protein intake also falls.

In all cases where underfeeding is persisted in for long periods it is associated with a smaller or greater loss of protein [Hirschfeld, Kumagawa, R. O. Neumann[1] (1)].

The best example is one given by R. O. Neumann. Starting with an insufficient diet, he very gradually and slowly raised the protein and energy intake until finally he arrived in nitrogen equilibrium. He kept on the insufficient diet for a comparatively long period, fully thirty-five days. The following table shows the conditions that existed :

Series.	*Duration in Days.*	*Intake.*			*Cal. per Kg.*	*Nitrogen Balance—*			*Difference in Weight.*		*Weight at Outset.*
		N.	Protein.	Cal.		Daily.	Of the Whole Series.				
1	10	8·02	51	1,535	23	-2·81	-28·1	-96·1	+0·0	-1·5	67·0
2	12	9·07	57	1,599	24	-3·11	-37·3		-0·9		67·0
3	8	11·24	70	1,909	29	-2·11	-16·9		-0·1		66·1
4	5	12·70	79	1,937	30	-2·76	-13·8		-0·5		66·0
5	15	12·23	76	2,659	40	+0·22	+ 3·3		+1·3		65·5
											66·8
	50	10·56	—	1,987	30	—	-92·8 (!)		-0·2 (!)		66·1

While the diet of Series 5, showing a moderate protein intake and sufficient energy value (76 grammes protein and 2,659 calories) was sufficient for the maintenance of nitrogen equilibrium, in Series 3 and 4, when the energy intake was diminished by 700 calories, considerable nitrogen losses occurred in spite of the protein intake remaining the same. The same occurred in the first and second series. Attention will subsequently be paid to the striking fact that Neumann, in the fifty days, with an average intake of 10·56 grammes nitrogen and 1,987 calories, lost 93 grammes nitrogen, and at the same time only showed a loss of 2 kilogrammes in body-weight.

It is unfortunate that we have, apart from Neumann's investigation, no long series carried out in healthy individuals with low intake—that is, the half or two-thirds of the normal diet, corresponding to 1,200 to 1,600 calories, and 40 to 70 grammes protein. Such a diet is frequently met with in the case of individuals suffering from disease. How much of the loss of flesh in such cases is due to insufficient food, and how much to the disease itself, we are not in a position to say, as comparable data in the case of healthy individuals are not obtainable. This is all the more important, as the conditions in health are so variable. Even in the domain of normal metabolism there are many difficulties in drawing up a general standard.

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[1] Bischoff, Voit, and others give numerous examples from the carnivora.

Anyone who carefully studies metabolic tables drawn up for different reasons, and compares them from the quantitative standpoint, will frequently be struck by remarkable results, which are extremely difficult to explain by any simple laws of metabolism.

In the following table a series of experiments is given which exhibits the different amounts of protein requisite for the organism, and also the necessary energy intake.

G. Renvall carried out a metabolic experiment with a different end in view from Neumann, and yet having one thing in common with the latter's experiments—namely, that he commenced with an insufficient diet, and gradually brought the food intake up to the body requirements. His experiment was also one of long duration (2).

Series.	*Duration in Days.*	*Intake—*			*Nitrogen Balance—*		*Difference in Weight.*	*Weight.*
		N.	Cal.	Cal. per Kg.	Daily.	Of the Whole Series.		
1	8	12·1	2,062	29	- 5·34	- 42·7	- 1·5	71·1
2	7	13·7	2,617	37	- 2·66	- 18·6	- 2·0	69·6
3	6	16·1	2,843	42	- 2·74	- 16·4	- 0·4	67·6
4	5	22·7	3,783	56	+ 0·14	+ 0·7	- 0·0	67·2
5	3	21·2	3,577	53	- 2·47 (!)	- 14·8	- 0·0	67·2
								67·2
Average	32	16·5	2,889	46·2	- 2·9	- 91·8	- 3·9	68·2

Renvall was only a few kilogrammes heavier than Neumann. He also was occupied with ordinary laboratory work, which, however, he found rather fatiguing. The arrangement of the investigation and the general results were the same in the two as far as concerned the principal points. Renvall's protein and caloric intakes were, however, about 50 per cent. higher than those of Neumann. After the preceding nitrogen deficit Neumann was able to attain equilibrium in the fifth series with 12·2 nitrogen and 2,659 calories (40·5 calories per kilogramme); while Renvall in the fourth series was only able to do so with 22·7 grammes nitrogen and 3,783 calories (56 calories per kilogramme). While the weight of the German increased 1·3 kilogrammes during this part of the experiment, that of the Norwegian showed no increase.

If one calculates the daily average during the fifty or thirty-two days respectively in the case of the two authors, one finds the same difference in requirements and consumption (see table).[1]

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[1] It is scarcely accurate to state averages for experiments where, in the individual sections, there have been marked variations in the protein and energy intake. Still, when the duration of the investigation is prolonged such a procedure is permissible.

Neumann and Renvall each lost about 92 to 93 grammes nitrogen in five to seven weeks, the former on a diet which would be considered barely sufficient under most conditions, the latter upon one which would certainly be regarded as rich, and yet the former maintained his weight almost unaltered. He must have stored water,[1] because it was impossible that any fat could have been put on under such a scanty dietary. Renvall, on the other hand, lost about 3 kilogrammes flesh (in addition to some water) and also fat—if, indeed, he had not put on the latter.

In the table on p. 340 there are included some other long series of experiments. Sivèn's second experiment, like those just mentioned, is one showing a gradual rise in the protein intake, but with a constant and sufficient energy intake. He only lost a small quantity of protein, with perhaps some fat and water, on a diet of the same caloric value (per kilogramme) as that of Renvall, but with only half the quantity of nitrogen.

In his first experiment, characterized also by sufficient caloric and scanty protein intake, but with the latter gradually diminishing in amount, he retained some protein on an average nitrogenous intake of 7·9 grammes (+0·3 kilogramme flesh put on ?). The loss of 2·8 kilogrammes is proportionately high for one of his build, and can scarcely be explained by loss of water alone (3).

The other investigations referred to in the table [Clopatt, Rosemann, (I. and II.), Neumann (II. to V.) (3)] were carried out, in contrast to the ones already described, on a constant and medium protein and energy intake. One would expect in their case approximately nitrogenous equilibrium and maintenance of body-weight.[2]

Clopatt, with an intake of 16·2 grammes nitrogen and 2,527 calories, retained some nitrogen, and his weight fell disproportionately, the loss being about 4·1 kilogrammes.

Probably he lost a large quantity of fat and some water. The gross caloric intake (2,300 calories = 31 per kilogramme) was evidently insufficient. A daily contribution of 75 grammes body fat would have brought his metabolism up to 3,000 calories (40 per kilogramme). From this one may reckon that he lost 2·7 kilogrammes fat and 1·4 kilogrammes water. In Neumann's fourth experiment (and also in others not mentioned in the table) the same is shown, and the final series in Experiment I. (see p. 340) shows a very low protein requirement.

In Rosemann's careful experiments 1·6 and 3·5 kilogrammes[3] were lost. With an intake of 16·7 nitrogen and 3,325 calories (= 41·6 per kilogramme) he retained daily about 1 gramme nitrogen, and yet lost 1·6 kilogrammes body-weight. With three-quarters of this protein intake, and with 90 per cent. of the previous caloric intake (12·8 grammes

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[1] It is scarcely credible that the slight loss in weight with great loss in nitrogen is to be explained by a decrease in the water-free "intracellular protein" (used in Lüthje's sense). Neumann certainly, on his extraordinarily low diet, could not have stored before the beginning of his experiment such quantities of intracellular protein.

[2] The fact that in five of these experiments an alcohol series was interpolated does not invalidate the calculations. It shows merely that the alcohol in this respect is without special influence (see the next section). In addition, the investigation was conducted for a long period after the alcohol experiments had ceased.

[3] Private communication.

No.	*Author* (3).	*Duration in Days.*	*Average Intake—*			*Nitrogen Balance—*		*Loss of the Amount stored.*	*Average Weight in Kg.*	*Period.*
			Nitrogen.	Total Calories.	Calories. per Kg.	Daily.	In the Whole Series.			
1	Neumann, I. ..	50	10·56	1,987	30·0	−1·85	−92·8	−0·2	66·1	March to May
2	Renvall	32	16·5	2,889	42·6	−2·9	−91·8	−3·9	68·2	October to November
3	Sivèn, II.	33	8·3	2,650	41·0	−0·35	−11·7	−1·6	64·7 (65·4–63·8)	(?)
4	Sivèn, I.	39	7·9	2.400–2,500	41·0	+0·27	+10·6	−2·8	59·4 (60·8–58·0)	(?)
5	Clopatt	36	16·2	2,527	34·0	+0·5	+17·3	−4·1	74·4	April to May
6	Rosemann, I. ..	29	16·3–17·1	3,325	41·6	+0·95	+27·8	−1·6	80·0 (80·8–79·2)	March
7	Rosemann, II. ..	24	11·7–13·5	2,966	37·1	−1·0	−23·3	−3·5	81·0 (82·5–79·0)	October
8	Neumann, II. ..	35	12·2	2,638	39·0	−0·6	−20·3	−0·1	68·5 (68·5–68·6)	—
9	Neumann, III. ..	36	18·0	2,958	41·0	+0·84	+30·4	+0·4	72·5 (72·3–72·7)	—
10	Neumann, IV. ..	24	12·2	2,638	39·0	+0·18	+ 4·3	+0·0	68·5	—
11	Neumann, V. ..	24	14·2	2,357	33·0	+0·0	+ 0·0	+0·15	71·5–71·65	—

Nos. 1 to 4: Variable amounts of nitrogen in the diet; in Nos. 1 and 2 (?) with insufficient caloric intake, in Nos. 3 and 4 with sufficient.

No. 1: Experiment with an insufficient nitrogen and caloric intake at the beginning. At the beginning nitrogen losses, at the end a slight gain in nitrogen.

No. 2: Similar to No. 1.

No. 3: Sufficient caloric intake throughout. Nitrogen intake at outset insufficient, rising to a free supply. At the beginning loss in nitrogen, at the end a gain.

No. 4: Sufficient caloric intake throughout. Nitrogen intake falling from a sufficient to an insufficient amount. In the beginning a gain in nitrogen, later a loss.

Nos. 5 to 10: During the whole course of the experiments an almost constant caloric intake.

Nos. 5, 6, 7, 8, 9: An alcohol series occurs in the middle of the whole investigation.

No. 10: Experiment with varying quantities of water (immediately following No. 8 in time).

No. 11: Experiment with myogen.

As a matter of fact, the nitrogen balance in all experiments is rather more unfavourable (to the extent of some grammes) than the numbers shown in the table. In no case was the loss by the skin estimated, and as this would amount at the least to 0·3 grammes daily the excretion of a thirty to fifty days series requires an addition of at least 10 to 15 grammes.

nitrogen and 37·1 calories per kilogramme), he lost about 1 gramme nitrogen daily, and 3·5 kilogrammes body-weight (water and fat ?).

The eleven experiments which have been quoted are selected with care, and may be regarded as absolutely reliable. They are, without exception, experiments carried out on the investigators themselves, who were working daily in laboratories under practically the same conditions. It may be taken for granted that errors or irregularities in the food consumption or in the collection of urine and fæces were as far as possible eliminated. The names of Neumann, Rosemann, and that of Tigerstedt (under whose supervision the rest of the work was conducted), are sufficient to guarantee the accuracy of the analyses. Therefore, the differences in the amount of nitrogen and in the protein and energy intake necessary to maintain equilibrium appear all the more striking. No attempt need be made to give an explanation of the conditions peculiar to the individual organization which produce these variable results.[1] It is sufficient merely to refer to the matter. Care must be taken, however, not to make false generalizations from the above results. The calculations are based on averages, and the conclusions drawn from these may not hold for each individual case.

The Protein Metabolism in the Underfeeding for Obesity.

The amount of protein loss in starvation or in underfeeding is not regulated solely by the quantity of fat in the body. Sivèn, who brought his nitrogen intake down further than any other investigator, was 60 kilogrammes in weight and 162·5 centimetres in height, and therefore by no means corpulent. The same holds good, with one exception, for Chittenden's twenty-six men. A person may accustom himself to larger or smaller quantities of protein, and this, doubtless, along with many other factors, plays in this matter an important part (4).

Still, as a general rule, a certain degree of corpulence prevents a great loss of nitrogen when the diet is insufficient. In corpulent individuals a caloric deficit in the diet less readily leads to protein losses, and, when these do occur, they are less than in the case of thin individuals. The possibility of effecting, by means of a low diet, the removal of excess of fat from the body without nitrogen losses, or with these very slight in degree, was proved in the first place by C. Dapper, after the unsuccessful experiments of F. Hirschfeld. Subsequently Magnus-Levy, Helleson, and Bornstein, published similar results. The process succeeds comparatively easily so long as the diet does not fall much below two-thirds of the requirements. A proportionately high protein intake (at least, compared to the individual's customary one) seems to favour the process [Dapper, Bornstein (5)] (see chapter on Obesity).

The well-known sparing action, which carbohydrates exercise on protein metabolism to an even greater extent than fats do, is also to be seen in the case of the diet cures for obesity. Helleson was able to show it distinctly in the case of a very stout girl twelve years of age. When starch replaced fat in the low diet the nitrogen balance could be more easily established, and the opposite occurred when fat replaced starch.

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[1] Compare "the luxus energy consumption."

Upon what does the favourable influence depend which is undoubtedly exerted on the nitrogen balance in starvation and underfeeding by a rich fat deposit in the tissues? One can only explain it by regarding the influence of fat in the tissues as of the same nature as fat in the food, and that when the body requires it, the fat cells yield up their excess of fat to the blood more readily and more rapidly in the case of a stout than of a thin person. Analyses of the fat present in the blood of fat and thin animals of the same type taken during a period of starvation might perhaps decide the question. It is true—and this remark holds good for other conditions—that the percentage amount of fat in the blood proves nothing with regard to the rapidity of the passage of the fat from its places of storage, nor with regard to its consumption by the cells which make use of it.

(For a discussion of the relationship between alcohol consumption and nitrogen metabolism, see later; for that existing between consumption of water and nitrogen metabolism, see the article on Water; and for that between sodium chloride and nitrogen, see Metabolism of Mineral Substances.)

(δ) The Significance of Protein Losses considered Chemically and Physiologically.

Technically, the section of pathological metabolism which is most easily studied is that concerned with the proteins. During the first ten to twenty years the work in this recently developed department was specially concerned with this particular subdivision. At present —so far, at least, as the metabolism in rest is concerned—the subject is practically closed, and our knowledge complete. The results so obtained form the groundwork for all further investigations. But it is also important to carefully avoid exaggerating the importance of work done on the significance of protein losses. Previously there was a great tendency to overestimate its importance, and this overestimation often obscured judgment. The significance of the decomposition of tissue protein from the biological standpoint is exaggerated, while from the chemical it is often falsely interpreted.

It was by no means uncommon to regard every sign of protein breaking down in disease as dangerous, and all grave symptoms as due to protein decomposition in the tissues. This is certainly in many cases a false conception. The signs of weakness often observed in unsuitable courses of treatment for obesity are certainly not exclusively the result of protein impoverishment. This is especially true for the defective cardiac action which is frequently noticed in cases where the weight is being too rapidly brought down. Cardiac muscle does not require protein to enable it to do work, nor does a loss of a few grammes in the case of the muscle lead to heart weakness. As a matter of fact, the heart loses but little when the rest of the body has lost much, unless it is very seriously diseased. The healthy heart loses but little in weight even after complete starvation of some weeks' duration. Numerous examples of this might be cited.

There is a second point often referred to which appears even less justifiable, namely, the erroneous significance which is often attached to the products of the decomposition of tissue protein considered chemically. Every possible product of pathological metabolism, whether appearing only in disease or increasing in quantity in pathological conditions, has been referred to as a product of the decomposition of tissue protein—thus, for example, the volatile fatty acids in acute yellow atrophy of the liver, acetone bodies in diabetes, etc., glycuronic acid, the still little-known toxines which produce coma diabeticum, or those which occur in Basedow's and many other diseases.

It is the usual but erroneous custom to group together insufficient nutriment with protein loss and abnormal metabolic processes because they are often observed side by side in severe diseases. But protein decomposition and pathological metabolic processes are not necessarily dependent upon one another. They are frequently associated with one another, but only as the simultaneously occurring effects of a disturbance of a higher order. Basedow's disease appears in spite of overfeeding [Hirschlaff (6)], and diabetic coma frequently occurs without preceding protein decomposition, and such a decomposition does not necessarily result from the coma [Magnus-Levy (7)]. That acetone bodies do not exclusively arise from protein has been definitely proved. There are, therefore, also other and perhaps more important sources of the volatile fatty acids and oxalic acid than the protein (6).

When we at present look back upon the work of the older writers, who placed every burden on the shoulders of the protein decomposition products, one is irresistibly reminded of Molière's satire on medical men, in that instance where all ailments of the hypochondriac were regarded as due exclusively to affections of the lungs. Even at the present day the decomposition of tissue protein is still regarded as the explanation of many unknown metabolic disorders. According to a very recent theory, the non-bacterial formation of indol and skatol can only possibly occur from tissue proteins, or, at least, is only to be observed along with protein loss. As the best investigation in this domain has recently shown, however, it is in starvation or in underfeeding that the conditions are most favourable for bacterial decomposition. And even if a non-bacterial origin of phenol and indol were granted, why conclude that they arise from tissue protein decomposition ? Where has it even been proved that tissue protein breaks down in a different way from food protein ? In all cases where so-called abnormal nitrogenous bodies have been met with in the urine in disease, these have been found to be the simple products of hydrolysis of protein, the same bodies which appear in tryptic digestion in autolysis and in the splitting of protein by HCl.

The same holds for such metabolic disturbances as are met with in the graver forms of disease. It is in such cases that we are asked to believe that, just as protein " melts away " in starvation, here tissue protein is of such a non-resisting character that it breaks down to furnish indol and skatol, which cannot arise from the protein of the food! Starvation is really a physiological event—as, for example, in the life of beasts of prey, and in that of such men as hunters. Must we take it that in these instances metabolism varies from its normal course,[1] with the result that the organism is threatened with a skatol or phenol poisoning?

The strongest evidence against this doctrine is one that is apt to be overlooked by its supporters, namely, that in the most perfect health tissue protein breaks down. The amount of food protein required for the replacement of the protein of the organs which breaks down during ordinary conditions is unknown, and the numbers mentioned in this book are, after all, only possibly correct. But no one doubts that there is a constant change in the protein of our tissues, although the amounts undergoing transformation cannot be accurately determined. The protein of the cells which undergo a breaking-down within the body is, with the exception of that belonging to the surface epithelia, split up and oxidized whether the individual be supplied with food or whether he be in a state of starvation. The daily amount of tissue protein decomposition on a normal diet is perhaps no less than the minimum loss in starvation (about 30 grammes) in the healthy person. Perhaps when a free supply of protein is given there is actually a greater replacement of tissue protein.[2] In this case the decomposition of tissue protein in the healthy person might be greater than in disease.

(ε) Energy and Nutritive Metabolism.

Increase of Metabolism, Improvement of Assimilation, etc.

Speck (8) has recently expressed very strongly the opinion that the metabolism is regarded as too exclusively an energy metabolism. This one-sided view of metabolism, condemned by Speck, can be easily explained. It is due to the fact that we can easily measure the amount of the energy exchange, while it is much more difficult to calculate the nutritive one. Much less are we able accurately to determine the part played by each constituent individually. With regard to the nutritive metabolism, our knowledge only extends to the consumption and replacement of the living tissue substance—*i.e.*, of the protein-containing protoplasm.[3] In this sense, the nutritive metabolism is very limited in extent, as has often been previously emphasized. Above all, attention has been directed to the fact that the food protein, the combustion of which amounts to at least ten to fifteen times the minimal quantity used up in starvation, only probably contributes a small and fixed amount for tissue protein. Speck's view, which differs in so many respects from that of others, undoubtedly gives rise to serious reflection in many respects. Although this be so, the chemical views which he propounds cannot be agreed to. The food protein, so far as it does not become tissue protein, in Speck's opinion, breaks down easily, while the tissue protein must first be set free by death from the seat of its organization before it can be attacked. This may be accepted without at the same time believing that the reason for this regular death of protoplasm is an oxygen deficiency. Speck further maintains that the tissue protein breaks down in a different way from the food protein, and that it furnishes different end-products. This abnormal direction of the decomposition cannot ordinarily be observed. It is only distinctly apparent in diseased conditions. Speck refers to a number of substances which are only derived from the breaking down of tissue protein—*e.g.*, uric acid, creatinin, lactic acid, acetone, etc. Any person conversant with modern chemical views will scarcely follow him in these points.

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[1] One does not speak of the absence of secondary oxidation in starvation, simply because carbohydrates are absent!

[2] The views of the older writers that food protein can supplant in full amount the tissue protein cannot be accepted; but it is impossible to deny that there may be a more rapid replacement of tissue protein when food protein is given in large quantity.

[3] In a certain sense the formation and storage of fat and glycogen may be considered as parts of a general food metabolism. Still, these are processes which are not absolutely essential for the maintenance of the ordinary vital processes.

More than twenty years ago Leichtenstern held up to derision certain mischievous views such as "the stimulated activity and metamorphosis of metabolism," "the building up and purification of the blood," etc. At the present day the doctrine of an "elevation of metabolism" is one that is in great vogue. The mystic belief in an improvement of assimilation and disassimilation appears to be one which attracts many supporters, and yet, so far as the nature of the processes is concerned, one finds evidence painfully lacking, and so far as quantitative alterations are concerned, there is no evidence at all forthcoming. A quantitative improvement in assimilation can only be affirmed in so far as an increased capacity of absorption on the part of the alimentary canal is concerned. In this way, at the best, one can only expect an improvement to the extent of a small percentage, leading to a certain improvement in energy exchange, to the sparing of stored material, and to an increase in the amount of reserve material.

Horace Fletcher (9) emphasizes the advantages of thorough mastication and good admixture of food and saliva. Since he has adopted these precautions in the ingestion of his food, he has been able to subsist on a much lower diet, and has kept in much better condition. This may be so, and yet the good effects may be due to other causes. Good mastication, slow eating, and the greater moderation which always then results, can only indirectly affect the body requirements.

We are not in a position to accurately define what is meant by an improvement in assimilation as regards metabolism. It is difficult to understand clearly how a diabetic patient on a constant diet can improve his general bodily condition by rendering his assimilation better.[1] An increase in the assimilative capacity of the diabetic patient for carbohydrates is spoken of, but that really signifies an improvement in dis assimilation. Under favourable conditions the diabetic patient acquires the power of breaking down the sugar molecule, and so gains a certain degree of benefit. Apart from this anomaly in metabolism, which concerns the withdrawal of one of the chief food principles, one can scarcely imagine an increase in assimilation or disassimilation benefiting the energy metabolism. Even in the case of the person suffering from disease almost all the potential energy in the form of absorbed food material is made use of, and even the healthy individual cannot gain more than 100 per cent. from his intake.

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[1] This does not refer to absorption. An improvement in *absorption* may occur, and may be of much importance, as in many cases of diabetes.

Our methods of investigation do not enable us to analyze the finer details in metabolism. The chemist, from an analysis of similar tissues in health and disease, can seldom recognise characteristic differences in the chemical composition of the protoplasm in the two cases. At most, these may be observed in diseases of the severest type ; but between the cells of a neurasthenic, anæmic, or rheumatic individual there are no characteristic differences.[1] The organism of these patients may improve when they are undergoing " cures " in Baden-Baden, Franzensbad, or Teplitz, but does this really depend upon the level of metabolism being raised—that is to say, on improved assimilation of the food ? Previously, no doubt was entertained that, when a patient suffering from Basedow's disease improved in the Engadine and gained in weight, it was due to the level of metabolism being raised. At present we know that after recovery from Basedow's disease the energy metabolism returns to the normal.

The doctor cannot easily free himself from the use of certain terms, such as the above mentioned, when he converses with his patient. From balneological and physiological nomenclature, however, they should now be excluded. Anyone who employs them should at the same time explain what he means by them.

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6. Hirschlaff : Morbus Basedowii. Z. k. M. **36.** 200. 1899. S. 186.

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[1] Alterations in the amount of hæmoglobin and similar changes are of course not referred to. The composition of the blood is one of the things which can, in some degree at least, be fairly well determined.

7. Magnus-Levy: Die Oxybuttersäure. E. Ar. 42. 149.—Magnus-Levy: Die Acidosis im Diabetes mellitus. E. Ar. 45. 389. 1901. s. S. 401.

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ADDENDUM.

Alcohol.

Although recently the benefits derived from alcohol in the treatment of disease have been regarded by many as very much overestimated, still, the fact that it is so commonly employed in the dietary both of health and disease, and also as a therapeutic remedy, should lead one to carefully investigate the part which it probably plays.[1]

Excretion of Alcohol.

Twenty years ago the predominant opinion was that alcohol was excreted unchanged, and this view was based, as so many others dealing with metabolism, upon false generalizations. At that time a quantitative analysis in investigations dealing with this subject was by no means usual. It is true that alcohol is met with in the excretions, but only in a very small proportion. According to Bodländer and Fr. Strassmann (1), when 50 to 100 c.c. alcohol are taken, 1½ to 6 per cent. are excreted in the expired air, 1 to 2 per cent. in the urine, in the sweat only traces, and none in the fæces. At least 90 per cent. (Strassmann), or 95 per cent. (Bodländer), was oxidized, even under the unfavourable experimental conditions. In the case of these investigators the alcohol was simply diluted with water, no food being taken at the time, and frequently slight intoxication symptoms appeared. Atwater and Benedict (1) investigated the excretion of alcohol under much more natural conditions: 72 grammes alcohol were given in six small portions distributed over the day, and given when other food was being taken. Under those conditions there was only a loss of 1·9 per cent., and it is with numbers such as these that one has to reckon in considering this question.

The Rôle of the Energy derived from the Oxidation of Alcohol within the Body.

The energy arising from the oxidation of alcohol within the body fulfils the following purposes: It is not *added to* the normal heat production, but spares the energy furnished from other sources (fats, carbohydrates). After alcohol, the oxygen consumption and the CO_2 output are but little affected [Zuntz and Berdetz, Geppert (2)]. This has been proved more completely by experiments of twenty-four hours' duration in the respiration chamber. Bjerres' daily metabolism on a day upon which no alcohol was taken was 2,043 calories; on the same diet, but with an addition of 168 grammes alcohol (!), it amounted to 2,328 calories. This increase of 14 per cent. was the result of a restless night. Clopatt used up on an "alcohol-free day" 2,101 calories, and on an "alcohol day" 2259·5—that is to say, 7 per cent. more. Atwater and Benedict found in twenty-six experiments, each of three days' duration, absolutely similar values for "alcohol" and "alcohol-free" days (2).

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[1] No reference will be made in this place to animal experiments. The isolated experiments, which appear to contradict the results just referred to, are those of Chauveau, which have been inaccurately carried out and their significance erroneously interpreted (see Rosemann).

	Rest.	*Work.*
Thirteen experiments without alcohol ..	2,190 calories.	3,664 calories.
Thirteen experiments with 72 grammes alcohol	2,191 ,,	3,696 ,,

This signifies complete isodynamic value of the alcohol during rest. During work also, at least 94 per cent. of its caloric value goes to replace other food-stuffs.

A most illustrative example from Atwater and Benedict may be quoted. A man received, in five-day periods, a fixed diet of 116 grammes absorbable protein and 2,290 absorbable calories, in Series 23 of the following table without any addition, in Series 22 with 72 grammes alcohol = 500 calories, and in Series 24 with 120 grammes sugar = 500 calories. The results of the experiments are shown in the following table:

Series.	*Intake.*		*Metabolism Calories.*	*Balance.*		*Retention in Calories.*
	Diet.	Gross Calories.		Proteid.	Fat.	
				Gm.	Gm.	
23	Fixed diet	=2,546	2,176	−1·6	+9·0	77
22	Fixed diet + 72 grammes alcohol (=500 calories)	=3,044	2,258	+1·4	+62·7	589
24	Fixed diet + 130 grammes sugar (=515 calories) ..	=3,061	2,272	+1·7	+59·7	562
22–23	Difference ..	= 498	+82	+3·0	+53·7	=512
24–23	,, ..	= 515	+96	+3·3	+50·7	=485
24–22	,, ..	= 15	+14	+0·3	−3·0	= −27

Alcohol can therefore replace equivalent quantities of carbohydrates or fats if the supply of these be insufficient—that is to say, can protect them from oxidation. If it is added to a diet that is sufficient, fat or glycogen are stored. From this it is seen that the significance of alcohol as a means of sparing other food-stuffs has been definitely proved.

Alcohol and Protein Metabolism.

Although alcohol can completely replace other nitrogen-free substances of like caloric value, still, it acts upon protein metabolism in a different way from fats and carbohydrates. It was thought at one time that alcohol had no protein-sparing powers, but rather increased protein decomposition. The first metabolic experiments, conducted by Miura (3), were in agreement with the latter hypothesis. On replacing 110 grammes carbohydrate by 65 grammes alcohol he observed in one series a total loss of 9·8 grammes on four "alcohol days," in another series 5·7 grammes nitrogen. The same losses were observed in experiments of shorter duration (E. Schmidt, Schöneseiffen), and also during the early days in those of longer duration [R. O. Neumann (I.), Rosemann, Clopatt (3)], but the losses were smaller than those given by Miura. When the experiments were prolonged, however, [Neumann (II.), Rosemann, Clopatt, Offer (II.)], it was found by the fifth to the sixth day that protein-sparing properties became noticeable, so that frequently the original losses were made good (3). G. Rosenfeld and Chotzen found at no time any protein loss, not even during the first days, and Neumann also, in his second research, when he began with small doses of alcohol, rising gradually from 20 to 100 c.c., obtained the same results. Therefore, after alcohol has been given for some time, there is certainly no protein loss such as Miura and the others described. It is also possible that those nitrogen losses which are frequently observed at the outset are not due to a breaking down of tissue protein, but rather to an excretion of nitrogenous waste products which leave the body more rapidly when alcohol is taken than under normal conditions (?). One must also remember that where protein losses have been marked, large amounts of alcohol have been taken, rarely under 72 grammes, usually up to 100 grammes or more. It is quite probable that even the initial protein loss is absent when such small quantities are taken as are customary in cases of invalids, to whom alcohol is given as a means of improving nutrition (*e.g.*, 40 grammes alcohol = 400 c.c. wine or 1,000 c.c. beer) [R. O. Neumann]. Habit also, undoubtedly, is an important factor, as with those who are accustomed to alcohol, the initial losses in nitrogen being less marked than in the case of total abstainers [Atwater and Benedict]. In the case of fever patients who have been previously accustomed to the consumption of alcohol, even larger quantities do not give rise to nitrogen losses (Ott). F. Hirschfeld's experiments on two diabetic patients with tuberculosis gave similar results (3).

With the exception of G. Rosenfeld and Ott, all agree that alcohol spares less protein than carbohydrate when both are given in isodynamic quantities, but in practical therapeutics this is really of no importance. The physician does not desire to make use of the protein-sparing properties of alcohol, but, on the other hand, he does desire to spare by its means the fat of the organism.

Attention must also be drawn to the fact that the utilization of the different food-stuffs is not affected by alcohol (Miura and others). Atwater and Benedict (4) give the following table, which shows the extent to which the food material is used up when alcohol is given :

	Protein.	*Fat.*	*Carbohydrate.*	*Energy.*
	Per Cent.	Per Cent.	Per Cent.	Per Cent.
Without alcohol ..	92·6	94·6	97·9	91·8
With alcohol .	93·7	94·6	97·8	92·1

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In Rosemann's two papers almost all the above experimental work is critically reviewed. v. Nr. 4. *cf.* Georg Rosenfeld, Der Einfl. des Alkohols auf den Organen. 1901; and Caspari, Alkohol als menschlich. Nahrungsmit. F. M. 1902. 1121; and Duclaux, L'Alcool et ses droits naturels. Paris, 1904.

4. Miura: s. Nr. 4.—Atwater u. Benedict: s. Nr. 1. P. 257.

C.—INFLUENCE OF MUSCULAR WORK UPON METABOLIC PROCESSES.

1. Muscular Work and Protein Metabolism.[1]

In an earlier chapter it has been shown that, although protein under certain conditions may furnish the necessary energy for muscular work, still, under ordinary conditions, it does not act as such a source.[1] Severe muscular exercise does not result in an increase of protein metabolism—at least, in proportion to the mechanical work which has been carried out [Fick and Wislicenus, C. Voit (1)]. In many cases there is no increase at all in the decomposition of protein. Still, muscular work is not quite without influence. Even Voit's researches, which were the means of destroying Liebig's theory, demonstrated this point. He noticed that the nitrogen excretion of the dog, both during hunger and when food was taken, increased slightly when work was done, but he laid little stress upon it. Argutinsky was the first to lay stress upon a rise in protein decomposition as a result of work. He found that during the day of active mountain-climbing there was no increase in the excretion of nitrogen, but that this occurred during the two following resting days. This had previously been overlooked, but since his paper was published numerous investigators have corroborated his results [Krummacher, Pflüger, Zuntz and Schumburg, Caspari, and others (2A)].

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[1] Energy Consumption in Muscular Work (p. 213); Source of Muscular Energy (p. 234).

The increase in nitrogen may amount to a number of grammes. Krummacher found after a day's march an increased excretion of 4·3 grammes nitrogen within seventy-two hours, after a two days' march one of 6·7 grammes within ninety-six hours. Dunlop and Paton give similar numbers, 5 to 8 grammes. In rare cases the increase in nitrogen excretion is even greater, rising in the experiments of Schumburg and Zuntz to 18 grammes in six days. In many cases it is true that no increase has been observed—for example, in the experiments of Oppenheim, F. Hirschfeld, Frenzel, and Kaup (2B).

Even if the increase be only observed in cases where the work has been severe in character, still, it in no way corresponds to the period of most active exertion. It is partly dependent upon the amount of labile protein circulating in the body, and thus is frequently greater on a rich meat diet than on one poor in nitrogen or in starvation. This inference may at least be drawn from the results of Voit's and Pflüger's researches (3).

A satisfactory explanation of the protein decomposition in muscular work has not yet been given. Oppenheim (4) held that it was caused by disturbances in oxidation, because he only observed the increase when the work was of such an exhausting nature that it led to dyspnœa (4). How far this condition is the cause of the altered metabolism requires still to be determined.

Undoubtedly other factors play a part. Frequently the rise is due to underfeeding, as in the majority of experiments care was not taken to add to the diet an amount of nitrogen-free food material sufficient to cover the increased work requirements [Voit, J. Munk, F. Hirschfeld (4)]. Even if the diet on the resting days was far beyond that required to cover the needs of the organism, it might have been insufficient when a large amount of work was carried out[1] [examples of this kind are given by Schumburg and Zuntz, Krummacher, Atwater and Benedict]. The losses were certainly smaller, the larger the amount of food taken on the working days and the greater the glycogen storage in the body. Also the diet of the preceding resting days influences the nitrogenous metabolism during work, because its extent is dependent upon the amount of glycogen that is stored. Thus, for example, a strong man in Krummacher's service lost 27 grammes protein when performing 324,000 kilogramme-metres of work on a diet of 5,000 calories and containing 136 grammes protein. When the caloric value of the diet was raised to 5,700 calories he only broke down 6 grammes protein more than in the resting period, although the amount of work performed had increased to 400,000 kilogramme-metres, and the protein intake was smaller than when the lesser amount of work was done. The researches of Atwater and Benedict furnish a most striking proof of the correctness of the above-mentioned view (4).

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[1] One can readily understand that, in cases where the work has been of an extremely strenuous character during a comparatively short period—as, *e.g.*, in severe Alpine climbing, in racing, etc.—the food intake does not cover the expenditure of energy. The American cyclists who, during the six days' racing, took 4,000 to 6,000 calories in their diet [Atwater and Sherman (4)], expended at the least 12,000 calories. But even here, where the food deficit was so great, the nitrogen losses were proportionately small, amounting to 8·6 and 7·1 grammes nitrogen in the day; thus far over 90 per cent. of the energy derived from material in the organism must have come from the body fat.

The fall in the nitrogen balance is a relative one in comparison with the resting days. If the balance were a positive one on the latter days, then the diminution that occurred on the working days only reached a stage where there was not necessarily a constant nitrogen excretion from the organism [Schumburg and Zuntz].

It is not absolutely certain that, in those cases where there is an actual rise in the nitrogen excretion (as in the experiments of Krummacher and many others), this loss is one of protein. From the fact that the nitrogen losses in most experiments are small, one is rather led to believe that the muscles, when called upon at the outset to perform a certain amount of work, discharge a small proportion of the extractives which they have stored. The parallelism between the nitrogen and sulphur excretion observed by Munk is, however, rather against this view, although not absolutely disproving it. The question as to the reason for the increased protein consumption during work and the significance of the rise has not yet been definitely settled (4).

All these facts apply to experiments during which work was carried out for comparatively short periods (one to three days), with a long resting period intervening. The conditions are different when work is continuously and regularly carried out for a longer period. Then the nitrogen losses not only become smaller from day to day (Pflüger), but finally even nitrogen retention may occur [Caspari, Bornstein, A. Loewy (5)]. Caspari brought a resting dog into nitrogenous and caloric equilibrium, then made it run daily for two hours up an inclined plane. He found that it lost 1·3 grammes nitrogen on the first day; on the second and third days nitrogen equilibrium was established; and then protein began to be spared upon each subsequent day until the retention amounted to 3½ grammes nitrogen in the twenty-four hours. During the period the body fat was freely used up to cover the energy requirements, as no more food was given during the working than on the resting days.

Bornstein obtained similar results from an experiment upon himself (5). On adding 40 grammes casein to a previously sufficient diet, more protein was retained during the working period than under similar conditions during rest. The nitrogen retention during the work period did not mount to such a high level as in the case of Caspari's dog, but the rise even during the last third of the eighteen days' series was higher than earlier in the experiment, while in the resting individual the protein retention after a few days became smaller and smaller.

One may safely say that in these experiments the nitrogen was retained as protein and as stable tissue protein in the muscles and elsewhere. This took the form of a hypertrophy due to increased activity of the muscles, a true hypertrophy in Virchow's sense of the term, the cells increasing in mass, but not in numbers [Morpurgo]. This protein storage during muscular work is undoubtedly the most useful one, and at the same time the one most conducive to good health. Caspari has shown that it may occur even on an insufficient diet, and protein retention can occur at the same time as a loss of fat. This investigator has directed attention to the importance of a knowledge of this fact in the treatment of obesity (5).

One need only expect to meet with such a favourable condition as nitrogen retention with loss of fat where the work that is performed is light in character, and not when it is excessive. In this connection the results of Atwater and Benedict's experiments may be referred to (5A). A man in the best of training (J. C. W.) covered about double the distance when cycling that the other individuals examined by Atwater and his fellow-worker were able to accomplish. His work expenditure was calculated at 2,700 calories, and he kept this up for eight days without the slightest strain. Whenever his food intake only covered 80 to 90 per cent. of his requirements, as was usually the case, he lost protein. He only maintained nitrogenous equilibrium in his last experiment, where his energy output was entirely covered by his intake of 3,000 calories.

A Satisfactory Diet for Work.

With moderate work and a free choice of food the individual, regulated by his appetite, usually selects a sufficiency of nutritive material to cover his requirements. It is not certain whether fats or carbohydrates act best as nitrogen-free substances which bring the working organism up to the necessary level for satisfactory performance of work and maintenance of the working mechanism. Extraneous conditions exercise a certain influence—for example, the temperature of the air, the volume and weight of the food-stuffs, habits, etc. The advantages of the fats consist in their high caloric value along with small mass, and the ease with which they are masticated. In the invigorating Alpine air, and in the low temperatures of the Polar regions, large quantities can be consumed with comfort. At one time inhabitants of these regions (woodcutters, mountaineers, etc.) preferred a diet consisting of fat and cheese to any other, although at present, with their social rise and increase in wealth, mountain guides are no longer satisfied with the same simple diet except in a few isolated places. As sparers of protein, when heavy work is being carried out, there can be no doubt that carbohydrates are surpassed by fats, although only to an insignificant extent [Atwater and Benedict (6)].

A question of more importance is whether the protein ration requires to be raised when severe work has to be carried out.

Moderate, continuous, and well-regulated work requires no increase in the protein intake, as may be seen from Chittenden's work (see p. 302). It is quite another question, however, whether, when an individual passes from light to severe work, it is not of advantage to increase at first the protein in the diet. If there is an advantage to be gained, in what does this advantage consist ? The question is still undecided, and has not in any way been settled by the elaborate researches of the American physiologists.

At present Voit's theoretical conclusion, which supports a dietary rich in protein, cannot be considered as decisive (see p. 305). The experience gained by those who train for sports is a safer guide. It is a well-known fact that in preparing for races the individuals, either of their own free choice or following the directions of their trainers, take large quantities of protein [Lichtenfeld (6)]. Still, it is doubtful whether this rule has always proved to be a beneficial one.

In Atwater and Sherman's researches intakes of 150 to 300 grammes protein are mentioned, when their proportion to the rest of the food was one-sixth to one-third—that is to say, a rather smaller proportion than is usually met with in the average dietary of the resting individual (6). It is not easy to decide whether experience here has proved itself to be correct—by no means a constant occurrence in dietetic matters—or whether tradition and racial customs do not play a part. Most of our information on this subject is derived from the English and Americans, who are in the habit of taking large quantities of meat. The vegetarian also, so far as our knowledge goes, is in the habit of taking such food preparations as will permit him to absorb a large amount of protein whenever he is called upon to do severe muscular work.[1]

On the other hand, an individual examined by Atwater and Benedict was able to maintain protein equilibrium for eight days on a daily intake of 110 grammes protein, when his diet, as in his last experiment (Nos. 52, 53), covered his energy requirements. His daily work amounted to almost 3,000 calories (6A)—a useful expenditure, therefore, and one worthy of attention being directed to it. The utility of a protein retention may show itself in two ways when the individual is called upon to do severe work : (1) in the prevention of protein loss ; (2) in the establishment of a higher functional capacity. These two modes of action can exist quite independently.[2]

As the nitrogen losses in severe muscular work usually result from an insufficient energy intake, these perhaps may be avoided by increasing the amount of protein in the food. This has often been observed in cases of underfeeding.

It appears, however, to be by no means absolutely necessary to prevent protein loss in severe muscular work. The loss cannot become too great, as it ceases if the work is continued for any length of time. Although there are no such conclusive experiments for severe work as Caspari furnished for moderate work, still, it may be taken for granted that the same holds good for the former as for the latter. Whenever the organism returns to its usual resting condition the losses are soon made good—so long, at least, as the previous strenuous work has not permanently injured the tissues.

It is a much more important question to decide whether a rise in protein metabolism may not raise the power of endurance of the individual to bear severe muscular strain. One must not simply think of an increase in muscular strength, but rather of a widespread effect upon the nervous system, increasing the general tonic condition of the tissues (see p. 239).

A comparison is often drawn, and as often misused, between the relative merits of the vegetarian and the meat-eater as working machines. The point of view is often an erroneous one; many conclusions that are drawn are superficial and deceptive. Still, it is justifiable to make the following statement, and to draw certain conclusions from it, that for similar size and muscular development carnivora are more capable of carrying out severe muscular work of short duration than are the herbivora.[1]

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[1] That is to say, even if no more protein be actually consumed, such varieties are chosen that a larger amount is absorbed than normally.

[2] Besides, we do not know whether a one-sided increase in protein retention actually prevents protein loss during work, or whether it merely conceals it. It is quite possible that a certain tissue might lose an amount of very important tissue protein, while in another part there might be a retention of absolutely useless protein.

It is a moot question whether this increased tonicity which has just been considered is dependent upon the increased protein metabolism, or whether the nitrogenous extractives also play a part in its production. It is also impossible to speak with any certainty about the necessity or suitability of an increased protein diet in severe muscular work. Although there have been numerous investigations on the subject, there are still gaps in the evidence, and certain points require further elucidation. In the near future the subject may be completely cleared up, because the present custom of an entire department being devoted to the elucidation of such a problem is one which is bound to be fruitful of the best results.

Sweat Secretion during Work.

During bodily exercise the nitrogen excretion in the sweat is large in amount, and in exact metabolic researches it must be taken into account. As a general rule, it increases proportionately with the amount of the sweat, and is therefore, just as the latter, dependent not only upon the amount of work, but also especially upon the degree of the heat loss. During similar tours, Argutinsky found that he excreted only 219 milligrammes nitrogen in sweat during autumn, while in summer the amount was 750 milligrammes or more. Zuntz and Schumburg obtained similar values after five to six hours' walking with knapsacks on hot summer days. In the underclothing alone 471 to 619 milligrammes nitrogen were present, while the sweat in the outer garments and in the body was not taken into consideration. A. Loewy noticed an excretion of 0·28 to 0·41 gramme nitrogen during work in the open, while Atwater and Benedict noticed an excretion of 0·2 to 0·66 gramme indoors. Cramer reckons that the excretion of nitrogen during severe work and in great heat may rise to 1 gramme and even more, and undoubtedly this is true. The larger proportion of this nitrogen is in the form of urea. Uric acid has not been found by most investigators to be present in the sweat during health.

In balance-sheets where the salts are considered, the NaCl excretion in the sweat must be borne in mind, as, according to Cramer, in severe work it amounts to 1·6 to 2·2 grammes NaCl during the day, and in the heaviest kinds of work, where perspiration is profuse, it may rise to 4·3 grammes (7).

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[1] Even the validity of this proof is questionable when one remembers the records of race-horses and the animals in Spanish bull-fights.

2. Muscular Work and Carbohydrates.

The carbohydrates are by no means the exclusive source of muscular energy. In so far, however, as they exist preformed in the body, they are freely used up during work, and thus the amount of glycogen in the muscle falls [Nasse, Weiss, Külz, Markuse, Manché, Morat, and Dufour (8)], and to a still larger extent, that of the liver. It is set free[1] during work, and passes to the functioning muscles as grape-sugar. This is immediately there consumed (if the work be prolonged), or becomes transformed into glycogen, and stored up for future work. Muscle, at any rate, holds its store of glycogen much more tenaciously than the liver. In muscular work, as in prolonged hunger, the liver glycogen may almost entirely disappear, while the muscles still contain proportionately significant quantities [Weiss, Aldehoff, Hergenhahn, Külz (9)]. Similarly, it is retained in arsenical poisoning [Rosenbaum], in phloridzin diabetes [von Mering], and in extirpation of the pancreas [Minkowski and Mering (10)]. Again, in fever, according to May, the muscle glycogen should be more permanent than that of the liver; yet Hergenhahn, by employing other experimental procedures, records the opposite condition (10). Very severe and prolonged bodily labour is necessary in order to cause the muscle glycogen to disappear entirely. Still more effective are the spasms produced by strychnine [Rosenbaum, Hergenhahn, Külz, Zuntz (11)].

Again, by diminishing the percentage of sugar in the blood circulating through muscles, one is able to demonstrate the using up of carbohydrate during work [Chauveau and Kaufmann, Quinquand, Morat and Dufour, Seegen (12)]. Under natural conditions of work one cannot well demonstrate the dwindling of sugar in the blood by a single[2] passage through the muscles. The difference in the percentage of the sugar in the arterial and venous blood of muscle can only be small. Here, as also elsewhere, the great velocity of the blood-stream prevents the occurrence of great differences. If, for example, a man would employ a necessary expenditure of 500 calories exclusively from grape-sugar in one hour's hill-climbing, then 130 grammes would be required for this. But during this period at least 500 to 1,000 litres of blood circulate through the functioning muscles; 100 c.c. of blood thus requires to lose only 26 or 13 milligrammes of sugar during the passage through the muscle, an amount which falls within the limits of analytical error. In a criticism of the work of Chauveau, Seegen has demonstrated how much care is necessary in judging the figures from such experiments. At the first impression Chauveau's rather vitiated and much too high values for the decrease of the sugar in the blood do not apply to normal relationships of work and circulation. The blood-stream was apparently retarded in his researches.

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[1] The primary diminution of the percentage of sugar during muscular work causes the gradual dispersion of the liver glycogen [Cavazzini (8)].

[2] Somewhat different is the question as to whether these small losses mount up, or in the course of work a diminution of the grape-sugar in the arterial blood follows in comparison with the percentage at the commencement of the work. That need not occur so long as a corresponding supply of sugar from the glycogen stores, etc., obtains.

In so far as muscle requires carbohydrate during work, it oxidizes it completely. A breaking up into smaller molecules, into lactic acid (or alcohol and carbonic acid), without subsequent taking up of oxygen does not liberate sufficient energy to furnish even a small part of the mechanical work. Nevertheless, the idea that during work grape-sugar is split up into lactic acid only is still frequently opposed. This ought, then, first of all, to be used up in the liver. One calls to mind the fact that lactic acid is always set free in muscle. In complete misinterpretation of Minkowski's brilliant experiments, it is concluded that the liver has " the task " of oxidizing the lactic acid formed in other parts of the body, since, after extirpation of the liver in an animal, large quantities of lactic acid appear in the urine. According to this, as Hoppe-Seyler has strikingly demonstrated, the liver must be the site of greatest heat formation in the body, although such a function is undoubtedly fulfilled by the muscles (13).

Up to now we cannot decide with certainty whether lactic acid is a necessary transition stage in the oxidation of grape-sugar in the muscles, or whether it thus arises here always in large quantity, to be afterwards consumed in another place and manner. It could then be only a by-product appearing in small quantity. Be that as it may, only small quantities of lactic acid are eliminated by the muscles so long as their blood-supply remains normal. One has certainly found in many experiments a distinct increase of the percentage of lactic acid in the blood and in muscle [Spiro, Markuse, Werther, v. Frey, Berliner-Blau, and others (14)]. But in the majority of these researches the circulation was impeded. More lactic acid is found the more unfavourable are the conditions of the blood-stream and the supply of oxygen [Zillesen, Araki, Hoppe-Seyler (15)]. Again, the striking experiment of Dreser, in which the acid-fuchsin saturating the muscles of a frog is reddened by their stimulation, was carried out with the circulation cut off. Thus, if lactic acid is really formed in the muscles under natural conditions of circulation and work, then certainly only small quantities appear in the blood and in the urine (see further under Urine).

3. Changes in the Blood during Muscular Work.

Water Loss from the Body during Work.

A small amount of the diminution of the alkalinity of the blood pointed out by the different authorities can perhaps be referred to an appearance of lactic acid in the blood during muscular work [Geppert and Zuntz, E. Peiper, W. Cohnstein, Drouin, G. Wetsel, etc. (16)]. If this decrease, as Cohnstein has shown, reaches a very great degree in rabbits, it may lead to their death, while in the dog it never exceeds a certain limit. This accords, therefore, with our knowledge of the diversity of the metabolism of acid in plant and flesh eating animals.[1] Geppert and Zuntz see in this diminished alkalinity of the blood the stimulus, or one of the stimuli which, acting on the respiratory centre, produce the increase of the respiration during work. The classical experiments of Walther, in which acids were administered to rabbits, and the study of the dyspnœic coma in diabetes, support this acceptation, and, in no less degree also, the experiments of C. Lehmann, who injected dilute phosphoric acid directly into the blood, and observed the consequent increase in respiratory exchange (16).

Geppert and Zuntz have shown that the arterial blood, in spite of the vast consumption of oxygen during muscular work, yields not less, but actually more, oxygen than during rest. In spite of accelerated circulation, the blood in the capillaries of the lungs can be almost completely saturated with oxygen. How the condition arises we have not to discuss here. The physiologists mentioned found that the percentage of carbonic acid was not raised, but rather generally diminished. Still, the general validity of this observation is limited by the contradictory results of experiments on the horse [Zuntz and Hagemann (17)].

Of further variations of the blood during work, those of the specific gravity and the number of the red blood-corpuscles have been more minutely examined. After a march of six to seven hours the specific gravity of the blood in man was raised about two to six thousandths —an average of 100 experiments. The number of red blood-corpuscles was raised about half a million [Zuntz and Schumburg (18)]. According to Willebrand, the same alteration has already appeared after muscular effort lasting ten minutes. There are, however, transient variations, occasioned by a thickening of the blood, which subside directly after the readjustment of the waste of water. At the conclusion of the two months period of marching the percentage of water and the composition of the blood were unchanged. In these healthy soldiers the originally healthy lymph was perfect, and not in need of more improvement. The changes observed immediately after the individual marches chiefly result from the loss of water, but are also partly due to the varying circulatory conditions in the skin. In the internal organs the percentage of water in the blood during work is perceptibly higher than in the cutaneous capillaries, as has also been found here and there under other conditions. The withdrawal of water is, in the first place at least, from the blood. In these experiments it frequently amounted to 2 litres in five hours. Zuntz and Schumburg consider that in this short time a complete adjustment of the osmotic pressure between blood and tissues had taken place. That, however, does not signify that the loss of water is distributed equally over all organs and tissues. The functioning muscles, instead of giving off water, rather become richer in water as the quantity of dissolved molecules in them increases. Their osmotic pressure rises up to the time at which they have taken up sufficient water [Ranke, Kurajeff, Ganiké, J. Loeb (19)].

After extraordinary exertion the loss of water from the body may amount to 2 to 3, or even 5, kilogrammes per twenty-four hours [Tissié]. Should, however, such severe work extend over several days, then such a great loss takes place only on the first day. On the succeeding days the body sets itself approximately on an equality with the supply of water, the body-weight sinking but slightly. We refer to the considerations in Atwater and Sherman's much-quoted experiment (20).

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[1] Still, the analogy of these conditions with those due to the administration of mineral acids in dogs and rabbits is not a complete one.

On the effect of the discharge of water-vapour during work, see the section on Behaviour of the Water in Metabolism.

4. Variations of the Urine in Muscular Work.

Quantity of Urine.

As the evaporation of water is greatly increased during severe work, and the supply of fluid does not keep pace with it, the amount of urine is diminished. The decrease lasts, at most, twenty-four hours beyond the day of work [Argutinsky (21)]. The loss of fluid must be replaced, so that a proportion of the water swallowed is retained in the body. The twenty-four hours' urine thus becomes more concentrated. It is surprising, however, that the specific gravity of the urine excreted during the work is not elevated, but reduced [Schumburg, Zuntz (21)]. In marching soldiers the diminution amounts to one to six thousandths as an average of numerous experiments.

Other Variations of the Urine.

The frequent appearance of albumin in the urine during severe work, in quantities up to ½ per cent., is in its essential features not always quite explainable [Leube, von Noorden, Senator, Albu, and others (22)].

Henschen's accurate researches make it probable that but rarely do small traces of albumin appear in the urine of healthy persons, however great their bodily exertions are. With this the experiments of Zuntz and Schumburg are in accord in every way, and particularly those of Giacosa, and of Atwater and Sherman, who in the most extensive records of trained cyclists never, or very rarely, observed albumin in the urine (22).

Next in order to albumin and globulin, an albuminous substance precipitable with acetic acid, which is at present generally regarded as a globulin, may be found [Matzumoto]. Noorden never found albumoses (23). Sugar also does not appear in the urine during work.

Distribution of the Nitrogen in the Urine.

The relative amount of ammonia in the urine is not increased by effort [F. R. Richter, Dunlop and Paton, von Noorden (24)]. This excludes with comparative certainty the passage of large quantities of organic acids in the urine. Thus, if somewhat more lactic acid really passes into the blood from functioning than from resting muscles, it is oxidized in other parts of the body. Its presence in the urine has been only rarely detected in a convincing manner [compare Heuss, Spiro, Markuse, Colasanti and Moscatelli (25)], and even then it only amounted to small quantities. The two Italian authorities, whose discovery is so often brought forward as most certain evidence, demonstrated only 0·46 gramme of zinc lactate in 13 litres of urine. Thus scarcely half a decigramme of lactic acid was excreted daily.

It is found more frequently, and in larger quantities, in tetanus [Wiebel], after epileptic seizures [Araki, Inouse-Sacki, Zweifel], and in strychnine-poisoning [Araki (25A)]. Here, however, the movements are inco-ordinated, the excretion of lactic acid being the result of overexertion and local want of oxygen. Whether regulated muscular activity of exhausting severity also leads to this in man would be well worthy of study.

Urea.—The relative amount of urea remains uninfluenced by very hard work, according to the records of Bleibtreu, Bayrac, P. F. Richter, Dunlop and Paton, Tissié, Oddi and Tarulli (26). Chibret Huguet alone reports a marked diminution. Kronecker and Jackson found the urea proportion of the nitrogen in old persons diminished as much as 42 per cent. In younger subjects it was normal or slightly diminished. This discovery deserves great attention if it be confirmed[1] (26).

Creatinin.—The estimates regarding the excretion of creatinin in muscular work vary considerably. This is due in great part to the difficulties of analytical technique, and partly to the fact that in the majority of cases creatinin and creatin are not simultaneously estimated. They can both be present in muscle and in urine. According to K. B. Hofmann, the amount of creatinin in the urine is not increased by work. Oddi and Tarulli obtained the same result with moderate exertion (27). Meissner observed a periodic delay of the excretion in this way—a diminution during the work was balanced by a subsequent excretory increase. On the other hand, Moitessier, Grocco, Gregor, and also Oddi and Tarulli, in severe work, at least, obtained a perceptible increase of the creatinin in the urine. The increase is at most not significant. The figures of Gregor appear the most reliable. He found—

(*a*) With mixed diet a rise of 0·99 gramme to 1·31 grammes.
(*b*) With non-flesh diet a rise of 0·35 gramme to 0·63 grammes.
(*c*) With non-flesh diet and fourteen hours' cycling a rise of 0·57 gramme to 1·34 grammes.

According to him the excretory increase is delayed beyond the day of work, or chiefly appears for the first time on the following days. Gregor considers creatinin as a final product of muscle metabolism.

The excretory increase of creatinin after excessive work can be brought into relation with an old observation of Liebig, who found an increase of the creatin of muscle after severe exertion. It amounted to ten times the normal average in hunted foxes. The accuracy of the result has been challenged by other observers, chiefly by Voit and Nawrotzky. On Liebig's side stood Saratow and others. Monari succeeded in confirming Liebig's meaning in its full scope. He took care to determine not only the creatin, but also the creatinin. The total of both was always raised in functioning muscle. The question of creatin metabolism is full of interest, and certainly deserves increased attention (27).

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[1] According to unpublished observations of A. Loewy, it behaves in this way under the influence of the air of high altitudes. He observed this also in younger persons.

The excretion of *uric acid* undergoes no essential variations during work [F. Hirschfeld, Herter and Smith, Dunlop, Laval, Tissié]. The metabolism of nuclein plays no rôle in this case. Moitessier alone holds the contrary (28). If bodily exertion be accompanied with marked perspiration, then more uric acid ought to be excreted, according to Laval.

One does not obtain a completely convincing picture of the effect of muscular work on the metabolism, and the changes in the functioning muscles, if one depends only on the daily excretions. The urine must be examined in shorter periods also. In this way Burian found that one hour's gymnastics would already lead to a moderate and soon excessive excretion of uric acid and purin nitrogen. If excised muscles of the dog are stimulated, and blood perfused through them, then the outflowing blood yields perceptible quantities of uric acid. The percentage of hypoxanthin rises in the stimulated muscles (28A).

The increase in the *acidity* of the urine during muscular work, which has been frequently affirmed [Klipfel, Sawiczki, v. Noorden, Aducco, Tissié], is most marked during and immediately after the work [Giacosa, Oddi, Tarulli (29)]. The small quantities of lactic acid which have been occasionally found do not explain the marked acidity of the urine. Other organic acids have as yet not been detected in increased quantity in the urine of the working individual. Perhaps this rise of the acidity depends upon an alteration of the relationship between inorganic acids and bases in the urine. This is not yet decided, for complete analysis of the salts during muscular work is still wanting. The researches have always comprised individual mineral substances only, and the results contradict one another in many ways.

Mineral Constituents.—G. Engelmann (30) was the first to describe an increase of the preformed sulphuric acid in the urine. The total excretion of sulphur in the urine runs parallel to that of the nitrogen. A unilateral increase or decrease of both the elements originating from protein does not take place[1] [J. Munk, Dunlop and Paton]. If more sulphur appears in the urine from increased nitrogen metabolism, then the increase involves essentially the oxidized and not the neutral sulphur [J. Munk (30)].

Munk concluded that a simultaneous increase of the excretion of lime and phosphoric acid in the urine and fæces results from a breaking down of osseous tissue. In consideration of the extremely small increase —it only amounts to a few decigrammes—one cannot share this view. Other authorities, like Kaup, found, on the contrary, a diminished excretion and an enriching of the body in these salts as a consequence of work. Most observers have wholly directed their attention to the phosphoric acid of the urine. They found either no alteration, or, rather, an increase, particularly in untrained people [Dunlop and Paton]. Yet the results of those researches which pay no attention to the phosphorus of the food and that of the fæces are to be valued only to a limited extent for their explanation of the altered urinary acidity. They are worthless for the determination of the metabolism of salts.

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[1] So far as the nitrogen excretion in the urine is not depressed by marked nitrogen waste in the perspiration.

The amount of sodium in the urine is lowered during excessive sweating [Dunlop and Paton]. This is to be understood in view of the great loss of sodium chloride in the perspiration, which may amount to 2 to 4 grammes, and even more [Cramer]. The excretion of sodium chloride in the sweat may become so considerable that the organism sustains loss and must again be supplied from the reserve on the following day of rest. Tissié's cyclist gave off 8·2 grammes of chlorine in the urine alone during a twenty-four hours' cycle tour—that is to say, more than he had taken in the food (specified for this day)—in addition to which was a non-determined quantity in 4 to 5 litres of sweat. The excretion of chlorine in the urine of the following twenty-four hours amounted to only 1·5 gramme with rich food (kind not specified). The excretion of the potassium is not influenced by moderate muscular activity [J. Munk, Dunlop (30)].

The explanation of many inconsistencies in the statements of authorities regarding the effect of work on metabolism is evidenced, after a closer examination, by the dissimilar extent of the work performed, and in the differences in the condition of the persons engaged in the work. Great exertion is still a physiological action depending on the extent of bodily exercise and the previous training of the body. It may be unhesitatingly accepted that exertion leaves the condition of the body as regards water, salts, and so on, unchanged in the long run. One may expect greater quantitative and qualitative deviations soonest with excessive exertion, and by too sudden transition from the period of prolonged rest to that of brisk muscular activity. So important are the differences appearing under such conditions for the comprehension of metabolism under sudden alteration of the mode of life that one will therefore be required to be on guard against applying the results thereby obtained to the processes occurring during normal muscular work.

5. Massage and Metabolism.

Slight as the immediate effect of massage is on the interchange of gases and the exchange of heat, so also is its action on other metabolic processes. The direct effect of massage has been extraordinarily overestimated.

If one bases the effect of massage cures on physiological investigations, and thus endeavours to understand them, then various conditions must be considered. The immediate effect, which appears during and immediately after the application, must be distinguished from the secondary effect, which asserts itself during the following hours or parts of the day. If the alterations in the total twenty-four hours' metabolism are traced, then like observations must be made upon the conditions which obtain in both the massage and the non-massage days. Not only must the assimilation of food and fluid remain unchanged, but the movements and the activity must remain unaltered. These conditions are not always taken into account by experimenters.

Diuresis was found to be increased by the majority of authors [Hirschberg, Le Marinel, Polubinsky, Bendix, Dunlop and Paton, O. W. Vogt (31)].

If healthy people with somewhat similar assimilation of food and fluid show a daily excretory increase of 100 to 200 c.c. during prolonged massage experiments, such an increase arises from a diminution of the water given off at other parts. It must diminish the skin perspiration, since the lung exhalation can scarcely decrease. Whether that really happens appears doubtful. It might be also thought that the organs yield an excess of water, owing to an improvement of their circulatory conditions; but this squeezing out of water from the tissues of healthy individuals can certainly last only a few days. Perhaps it plays a rôle during the very first days. Accurate daily weighing of the body may give evidence of this. Such figures are, unfortunately, not available.

Hirschberg noticed that the daily urinary amount was increased about 500 to 2,000 c.c. after two to four days' massage. Increases of this extent must depend upon a more liberal supply of water, or upon an absorption of œdema. In the sick patient other relationships come into play more than they do in the healthy.

Bum explained the increased diuresis by the fact that substances were expressed out of the muscles by massage, which might stimulate the kidney to more marked excretion. In experiments on animals, he found that the urinary excretion was more marked during the five to fifteen minutes' massage than immediately before or after (31). But the rise of the twenty-four hours' urinary amount stated by many observers is not to be explained alone by the briefly lasting increase during the massage. It must have still other causes.

The nitrogenous metabolism is not much influenced by massage. Zabludowski first carried out experiments on three patients, whom he massaged for ten days. An average of the individual results shows no alteration of the excretion of nitrogen and sulphuric acid. Keller and Bendix, in experiments which are newer and better performed technically, observed during three to nine days' massage-cures a daily excretory increase of about 1 gramme of nitrogen in the urine. O. Vogt noted the same quantity, but the effect diminished with frequent repetition of the massage. Dunlop and Paton did not detect any effect after one day's massage. The increase of the protein metabolism in Gopadses' students amounted only to 1 to 4 per cent., and thus lay within the limit of the physiological fluctuations.

The absorption of nitrogen was somewhat improved in the experiments of Gopadses, as also in those of Kijanowski. In contradistinction to both these workers, Bendix found with massage a few decigrammes more nitrogen in the stool than in the preceding period. The fæces contained somewhat less fat in this case. Bendix, on the ground of his "experiments," accepts a very pronounced secretion of digestive juices and an increased absorption from the intestine. There is little inclination to agree to this "explanation." It is more satisfactory to register singly the results which can be obtained in many other ways, and which in addition lie within the limit of physiological fluctuation. The same remark may be applied to Beccarini's report upon a patient who, although the diet was unaltered, excreted an increased amount of ethereal sulphates and indican as a result of abdominal massage.

More worthy of notice is a discovery of Keller (31), who observed an increase of the chlorine excretion. The food in his experiments contained only a small percentage of sodium chloride. The chlorine excretion should therefore have been diminished. Here one could, with the author, actually imagine a marked "squeezing out" of the chloride-rich lymph from the tissues. When the water plus chloride in other parts of the organism is not used up it is excreted. The absolute increase of the chlorine excretion is not significant. It is of little importance, as the percentage of chlorine in the urine became diminished in consequence of the small proportion of salt in the food. With increased salt in the food the small rise in the urine would have been overlooked. It might be recommended for further study of the effect of massage on the metabolism of nitrogen and the salts to supply only small quantities of both in the food, quantities, however, which are sufficient for the needs of the body. Eventual alterations will then be brought out more sharply than with a rich supply, while their interpretation will be simpler (31).

Finkler, many years ago, found that with massage, as also with muscular action in diabetes, there was a diminution of the sugar in the urine. A very careful investigation by Seichter, from Mering's school, has, however, not confirmed the general applicability of this procedure.

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D.—INFLUENCE OF SEXUAL PROCESSES ON METABOLISM.

1. Menstruation.

(a) *The Protein Metabolism.*

Of the researches on the behaviour of protein metabolism during menstruation, those of Th. Schrader are of especial value (1). When sufficient food was administered, this author found a retention of several grammes of nitrogen, partly immediately before and partly during the period. He explained the retention as an appropriate economy in view of the loss of protein with the menstrual blood. All other observers have neglected to bring the women examined by them into nitrogenous equilibrium ere they searched for alteration of the nitrogen balance during menstruation. They gave only a diet "similar as far as possible." Their results are thus in no way certain. Rabuteau observed a diminished urea excretion during the menstruation, and Jacoby an increased urea output during the premenstrual period. Ver Eeke records, on the one hand, a moderate decrease of the urea excretion before the period, and, on the other hand, a rise of 6 to 8 grammes of urea above the average (hypobromite method!) in the first days of the monthly flow. The increase varied directly with the amount of blood lost (1).

The researches on animals are technically more accurate. In bitches, Potthast, who, in fact, interprets his figures in other ways, demonstrated a slight nitrogen retention during the "heat." The same occurred during the first days of the decline in Hagemann's experiments. After covering, however, there was a loss of nitrogen. Relatively much nitrogen was retained by the bitch during heat [Schöndorff]. In rabbits, on the other hand, ver Eeke noticed perceptible losses of nitrogen (1).

While Schöndorff draws the same deductions from his results as does Schrader, ver Eeke refers his contrary observations partly to unknown influences of menstruation, and partly to the loss of blood which occurs. The second portion of his argument invites further discussion. Several authorities like Jürgensen, Bauer, and ver Eeke himself have distinctly observed protein loss after withdrawing blood in well-devised experiments, but still, only after blood-letting so extensive as to equal about one-quarter or one-third of the total quantity of blood in the body. This marked loss of protein did not occur with smaller quantities. That, perhaps, also explains the contradiction between the results of von Noorden, who noticed that moderate hæmorrhages from the stomach did not affect the protein balance, and those of H. Strauss, who found in the same condition a marked loss of nitrogen four times out of a total of seven cases.

Prussak gives the menstrual bloodl oss in healthy Scandinavian women as 50 to 150 c.c. This is so small a percentage of the total blood that the escape would scarcely of itself produce an increase of the protein metabolism (2). Still lower are the figures which G. Hoppe-Seyler has recently published. From his colorimetric estimations, the hæmoglobin excreted during a normal menstrual period represents 26 to 52 c.c. of blood, in which are certain quantities of serum and mucus. With abundant and irregular quantities of blood the loss is higher.

Lüthje incidentally observed that an increased nitrogen metabolism due to an excessive nitrogenous and fat intake was not diminished during the period (3). The patient, weighing about 60 kilogrammes, received daily 200 to 300 grammes of protein and 3,000 to 4,000 calories. She metabolized daily 18·6 grammes of nitrogen—that is, just as much in the preceding period as during menstruation (! ?)—in spite of an extraordinary loss of blood during the menstruation. The unusual extent of the blood loss in this case was, in our opinion, the result of the preceding extensive storing up of nitrogen (3).

(*b*) *The Behaviour of the Salts.*

The excretion of phosphoric acid and chlorine in the urine of animals and of man during the menstrual period does not present anything characteristic. Both run closely parallel to the excretion of nitrogen [ver Eeke, Schrader (4)].

The absorption of nitrogen and fat was mostly normal in the experiments of Schrader and Hagemann. Also in Lüthje's experiment the using up of the quantities of protein supplied in excess was not impaired during the menses (4).

(*c*) *The Exchange of Energy.*

The theory of the *Wellenbewegung* (wave-like periods) in the life of women [Reinl], in its dependence upon the sexual phases, has given occasion to many premature conclusions upon the behaviour of the metabolism. In reference to the protein balance, the question is not yet decided. The exchange of energy in rest, the minimal exchange, is not, at least, influenced by menstruation. Leo Zuntz, in numerous experiments, found, in contradistinction to the intermenstrual period, the absorption of oxygen and the excretion of carbonic acid to be unchanged both before and during the menstrual period. The fluctuations which occasionally appear lie within the limits of error of such experiments. The results of H. Salomon concur throughout with those of Zuntz (5). Recently Zuntz (6) has observed a regular lowering of the temperature during the menstrual period (0·3 to 0·45° C.). When the period was ended the temperature rose gradually to the normal. He also records a diminution in the pulse-rate.

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2. Metabolism during Pregnancy.[1]

The most important question in this connection, which concerns the behaviour of the maternal organism during the elaboration of the embryo, is frequently considered in the following form: Does the mother build up the infantile organism exclusively from the materials which she draws from the food, or does she supply to the child material from her own tissues?

From this standpoint the question possesses great theoretical interest. It signifies something other than that for which it is of the first importance to the investigator. It is clear that a tissue can build itself up from the materials of another tissue. There exists no doubt that, with insufficient nourishment, and perhaps also under normal conditions, a portion of the organized protein can pass over from the mother to the germ. Just as certainly, however, can the protein of the food of the mother also become directly requisitioned for the building up of the embryo. It does not appear to be absolutely necessary, however, that the material in the maternal organism become first elaborated, and that the different albumins must be conveyed already prepared to the embryonic body in the placental blood. For in all embryos which develop in eggs the building up of the different highly organized protein ensues from less simple ones, and without the assistance of the maternal animal.

Of greater and more practical importance is the question whether the expenditure associated with the growth of the germ, etc., entails loss to the mother or not. If the mother must transfer a part of her own bodily substance to the germ, the loss is of little importance if she can cover this loss from the food. The setting of this question runs thus: Is the maternal body deprived of protein, fat, and other substances during and in consequence of the formation of a new being, and is its store of these materials, after the resulting birth, or at the close of the puerperium, less than before the advent of pregnancy, or is this not the case?

[1] See also a review (with bibliography), in B. M. J., 1906, p. 1534.

An unprejudiced clinical proof from human subjects points to the possible occurrence of both conditions. Many mothers during pregnancy increase so slightly in weight that their own tissues must certainly have suffered loss during this time. Others become heavier to the extent of 10 kilogrammes and more during this time. The investigation has not to determine whether the maternal organism suffers loss or experiences gain, but to demonstrate under which conditions of nourishment the one or the other appears. It has to investigate whether, and in what amount, the needs of the mother are increased, if her original condition is to remain unaltered while new tissues are being formed.

(*a*) **Protein Metabolism during Pregnancy.**

The demonstration of an exact nitrogen balance during the entire period of pregnancy is necessary. Such a balance has only as yet been conducted on animals during brief periods of pregnancy.

(*a*) *Nitrogen Balance of the Entire Pregnancy.*

Three attempts have been made which, although they have not overcome all the difficulties essential to the nature of the task, nevertheless may be characterized as exact investigations. They are the experiments of Hagemann and Jägerroos on bitches, and of ver Eeke on rabbits (1). It was in the first place important to decide whether, and how much, nitrogen was retained in the body of the pregnant animal from the food during the whole pregnancy (nitrogen of the food minus nitrogen in urine, fæces, hair, etc.). Then, immediately after birth, the amount of the nitrogen stored up in the young was determined, the nitrogen in the maternal placenta and the liquor amnii ascertained, and also that lost in the blood during birth. It is not possible to directly succeed in determining these three last articles, as it is so difficult to prevent the mother animal from devouring these products, and their protein becomes again conveyed to the body as nourishment.

If the total amount of the nitrogen discharged at birth exceeds the amount of nitrogen retained by the maternal animal from the food during pregnancy, then pregnancy ends with a loss of nitrogen on the part of the mother, and with a gain if the reverse be the case. The five examples (p. 372) from ver Eeke's work show how the different conditions may occur.

Subject No. 1 shows the " optimum ": the animal has, besides the nitrogen transferred to the young, still deposited protein in its own body. No. 2 has devoted all the nitrogen economized during pregnancy to the building up of the offspring, but at the same time has kept its own body in nitrogenous equilibrium. In Nos. 3 to 5 the pregnancy ended with a loss of nitrogen for the mother, so that the three cases behave differently. The fourth rabbit has again excreted all nitrogen of the food in the urine and fæces during the pregnancy. Thus exactly as much nitrogen was lost from its own body as was necessary for the building up of the tissues of the young, etc. In No. 3 the conditions for the maternal animal were not so unfavourable, as it had retained at least some nitrogen from the food during pregnancy. They were, on the other hand, most unfavourable in the fifth animal, which must not only have built up the young "from her own body," but have experienced in addition losses in tissue protein.

Rabbit.	*Nitrogen Loss or Gain—*		*Nitrogen Balance.*	*Remarks.*
	In Urine and Fæces during Entire Pregnancy.	At Birth through the Fœtus.		
	Gm.	Gm.		
1	+ 10·57	− 6·67	+ 3·9	Nitrogen gain by mother.
2	+ 5·47	− 5·06	+ 0·4	No nitrogen loss by mother.
3	+ 4·11	− 9·89	− 5·8	Nitrogen loss by mother is less than the nitrogen contents of fœtus.
4	+ 0·36	− 5·97	− 5·6	—
5	− 6·3	− 7·5	− 13·8	Marked nitrogen loss by mother.

In these figures the nitrogen loss with the placenta is not included. The nitrogen balance is really not so favourable in this table as our explanations suggest.

The animals represented under Nos. 2 to 5 received exactly the same food before and during the pregnancy. The nitrogen balance in the "period of sexual rest" was much more favourable than during the pregnancy. In order to obtain the optimum in No. 1, ver Eeke must have allowed the animal to eat freely after covering. In this way it had assimilated more food than in the preceding period.

Daily Nitrogen Retention from the Food.

	1.	2.	3.	4.	5.
Before the pregnancy	+ 0·145	+ 0·262	+ 0·333	+ 0·194	+ 0·301
During the pregnancy	+ 0·342	+ 0·177	+ 0·132	+ 0·012	− 0·210
	Unlimited supply.	Moderate supply of food before and during the pregnancy.			

Thus, in spite of the fact that the mother had to provide for her offspring during the pregnancy, the animal retained from the food in this period less rather than more nitrogen. That does not indicate a special "economy of protein" metabolism in pregnancy. The following consideration will make this clear: If one diminishes the amount of protein in the food about 10 per cent., but maintains an average supply of protein and of calories, the protein metabolism is hardly at all affected. In the first days a small amount of nitrogen is lost, but after a short time nitrogenous equilibrium again obtains. A greater or less supply to the extent of 10 per cent. of an average amount of albumin does not, in the long run, essentially influence the stock of protein. It is to be expected that the pregnant animal, if it transfers 5 or 10 per cent. of the absorbed nitrogen to the young, must then completely provide for its own needs with the remaining 90 per cent. In like manner, apparently, behaves the patient with nephritis who excretes 5 to 10 grammes of albumin daily in the urine, and the patient with cirrhosis of the liver, who discharges per diem 15 grammes and more into the peritoneal cavity. Both are able to maintain the nitrogen store of their organs unaltered—a fact satisfactorily determined for many cases.

Were the same the case in pregnancy an objective sparing of the protein economy could be described. Heretofore this has frequently been accepted without adequate proof. In ver Eeke's experiments the condition was not present during pregnancy. Hence the marked nitrogen accumulation before the period of pregnancy must be considered as an appropriate preparation for the subsequent period with its increased expenditure. This idea has much to commend it.

In Hagemann's experiment (1) the food, with its average percentage of protein and large percentage of calories, was perhaps directly sufficient to render the building up of the offspring possible without the mother losing nitrogen. Under similar conditions of nourishment, however, Jägerroos' first bitch at the end of parturition had lost over 60 grammes of nitrogen. Also, in his third animal a rich flesh diet did not prevent nitrogen loss, while only in his last case, with a diminished supply of protein, were evidences of a certain economy of protein metabolism present.

From these statements, considering the whole duration of pregnancy as a unit, the only conclusion possible is that a special sparing of the protein economy does not exist in pregnancy. On the same amount of food, the mother animal retains less nitrogen for itself and the young together than for itself alone in the non-pregnant condition, and so loses nitrogen on the whole period.

In order to be able to build up the infantile organism without simultaneous damage to its own tissues, the maternal organism must supply significantly large quantities of protein. The contribution must, apparently, be very much higher than the amount of nitrogen which the young and the placenta, etc., represent. As yet no accurate investigations exist regarding the extent of the necessary extra requirements.

(β) *Nitrogen Balance of Certain Periods of Pregnancy.*

When certain definite periods are investigated, instead of the whole pregnancy, the nitrogen balance occurs at the time when the growth of the offspring and the fœtal appendages, etc., makes the greatest demands —namely, in the second rather than in the first half [Jägerroos, Hagemann]. Here a retention of nitrogen usually takes place, which suffices to cover the whole protein requirement of the developing embryo, etc. Consequently the organism of the mother animal in the first period of pregnancy appears to adapt itself to the altered conditions with marked loss, while more favourable results appear in the later months.

For the conditions in the human subject, examples are called for from the various months of pregnancy. The foregoing evidence is scanty and insufficient. The previous investigations on excretion of nitrogen and urea in pregnancy, etc., do not include a consideration of the food and the fæces, and are therefore of little use for the purpose in view. Singly and alone, Zacharjewsky (2) has estimated the amount and contents of the food, and thus found himself in a position to determine the nitrogen balance for the last two weeks of pregnancy. With food fairly rich in nitrogen (its caloric standard unfortunately does not permit of being calculated from the summarized statements) perceptible amounts of nitrogen were retained practically without exception, on an average 0·873 gramme daily in primiparæ and 5·05 grammes in multiparæ. The latter ate rich food freely. The strikingly high economy of nitrogen on the day before birth appears important (between 5·3 and 11·1 grammes, with a single but only apparent exception). This must clearly be attributed to the preparation for birth ; in any case, it cannot be interpreted as a purely mechanical retention, since the amount of urine of that day was raised rather than lowered. Again, the investigations of Schrader (2) indicate a retention of nitrogen in the last six weeks of pregnancy with food rich in nitrogen and calories. Schrader's figures are not, however, sufficiently conclusive ; he did not analyze the food, and certain errors have crept into the calculation of the nitrogen percentage (2).

(γ) *The Absorption of Food in Pregnancy.*

In the periods of pregnancy just mentioned only 4 to 6 per cent. of the nitrogen was unabsorbed [Zacharjewsky ; slightly more according to Schrader (2)]. In dogs the absorption of meat scarcely deviated from the normal during the whole period of pregnancy [Hagemann, Jägerroos (1)]. Only in herbivora was the absorption of nitrogen perceptibly less in the second half of pregnancy (ver Eeke ascribed it to mechanical conditions). The absorption of fat and of the other food-stuffs is apparently not essentially altered ; at least, the amount of the fresh fæces in most experiments on man and dogs was not more than the average.

(δ) *Requirements of the Mother for the Daily Growth of the Offspring.*

The increased requirements of the pregnant female, in consequence of the building up of new tissues, is frequently overrated, as also are the demands of the young growing body. The requisition is spread out over long periods, that of a single day being slight. We may leave it undecided whether the developing and the pregnant organism need more material for the work of organization itself,[1] and give in the following only an estimate regarding the amount of material deposited in the embryo. A comparison of the weight and composition of the fœtus with that of the full-term child will allow us to form an idea of the amount of food-stuff required for this period of development.

How great the increased requirement in food-stuffs for the growth of the offspring is, permits of being best gathered from the statements regarding the composition of the fœtus and the newly born.

This is thus the time in which an essentially increased supply of food-stuffs is necessary for the mother. Still, one ought and must not over-rate the daily intake. I calculate the increased demand only for these months.

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[1] From the investigation of Scandinavian observers on the consumption of energy in incubated eggs, the work of organization itself appears to require no specially great discharge of heat (17).

The average daily deposition in the fœtus for the last hundred days represents not more than 3·0 grammes of protein, 3·5 grammes of fat, and 0·6 to 0·75 gramme of salts.[1] The daily increased requirement of the mother is certainly somewhat greater, as the uterus, the mammæ, etc., must also increase correspondingly with the growth of the offspring. The growth calls for protein in the first place. If we estimate the quantities necessary for herself, then the increased requirements of the mother necessary for the building up of new tissues in comparison to the needs of her own body are really still quite insignificant.

	Weight.	*Dry Weight.*	*Nitrogen Contents.*	*Fat.*	*Ash.*
	Gm.	Gm.	Gm.	Gm.	Gm.
Embryo (7 months)	900–1,000	150–160	16·0	26·0	26·0
Fully-grown fœtus ..	3,200	850–1,000	60–65	350	85–100
Addition in about 100 days	2,250	700–850	45–50	350	60–75
Average per day ..	22·5	7–8·5	0·45–0·5 =about 3·0 albumin	3·5	0·6–0·75

Thus the greater part of the dry weight—viz., about 75 per cent.—is added during the last three months of intra-uterine life. The addition chiefly consists of nitrogen and of salts (earthy phosphates).

(*b*) Protein Metabolism. Parturition. Puerperium. Lactation.

On the day of birth, Zacharjewsky observed fairly large losses of nitrogen, and less in the subsequent four to five days of the puerperium (4). In this period, lying-in women do not take sufficient food even to cover the increased discharge of nitrogen by the lochia and in the formation of milk. With richer diet, nitrogenous equilibrium was reached in almost all cases on the fourth to the sixth days of the puerperium. Subsequently there was retention of nitrogen. Two lying-in women on the eleventh day had already made good the preliminary waste, in spite of the fact that they nursed their children. With others this was not the case. Three mothers had lost 10 grammes of nitrogen by the seventh day of the puerperium, while four others in nine to ten days lost 25 to 42·9 grammes. The favourable nitrogen balance of the former was not exclusively the consequence of a rich supply of protein, but depended chiefly on the condition of the body. In one case, with only 14 to 22 grammes nitrogen in the food, the puerperium closed without waste of nitrogen. Another case, with 22 to 34 grammes nitrogen loss, on the other hand, lost 25 grammes nitrogen. Robust peasants maintained their condition much better than did weakly town-dwellers.

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[1] These figures do not represent absolute values applicable to all cases, as the age of the offspring was but rarely accurately known, nor the influence of external conditions upon its general composition. The statements on the increase of weight of the fœtus in the last two or three months vary according to the individual authorities. The composition of the newly born is always different according to its length, weight, and the extent of development.

The experiments of Zacharjewsky show, in fact, that the nitrogen balance in the days before and after birth can be normal, but as the percentage of the food in fats and carbohydrates is not furnished in the figures, it is impossible to say whether the organism in this period really deals more sparingly with protein than otherwise (4). Ver Eeke's experiments on rabbits proved that at the commencement of the puerperium, in spite of sufficient food intake, nitrogen was still lost. The protein arising from the genital organs during involution is thus excreted without being consumed in the body—that is, without sparing the protein of the food.

During the period of lactation also, the mother animal has, just as during pregnancy, to provide for the preservation and growth of the young. Thus, she must excrete less nitrogen by the urine and fæces than is present in the food, in order to preserve nitrogenous equilibrium, and at the same time cover the amount present in the milk. This may happen even if the intake is not raised. Yet in Hagemann's experiments (5) the nitrogen retention was less than what was secreted in the milk. The bitch lost nitrogen, while the puppies increased in size. According to Jägerroos, on the other hand, the mother animal retained more nitrogen from the food than it gave to the sucking pups, and therefore protein was retained in her tissues. After the removal of the young a period of more profuse protein retention followed, according to both authorities (5).

(c) Respiratory and Energy Exchange during Pregnancy.

The results of the few investigations already made all point to an increase of the gaseous exchange during pregnancy, yet the observations do not provide too reassuring conclusions. Oddi and Vicarelli (6) found in gravid rats in the last third of the period of pregnancy (from fourteen to twenty days) a progressive increase in the consumption of oxygen, and a somewhat greater increase in the amount of carbonic acid expired. Repreff records opposite conditions in the rabbit, guinea-pig, etc. These experiments upon animals, each lasting six hours at most, yield unreliable results, as the movements of the animals were not regulated, and were probably not equal in the several cases.

In 1843 Andral and Gavarret published results obtained from human experiments, and then sixty years elapsed before further investigations were undertaken [Magnus-Levy (6)]. The figures of the French workers relate to different women at various stages of pregnancy. As a normal and comparative standard, they employed the gas exchange of non-pregnant women, and not that of the same women in the non-pregnant condition. The gravid females excreted more carbonic acid than did the unimpregnated; but the evidence adduced does not permit proper comparison, and, in addition, the weights of the women are not stated.

The only accurate method of experiment is to study the gas exchange in the same person under normal conditions, and then to trace it through the whole period of pregnancy and during a few months after parturition. Adopting such precautions, Magnus-Levy found the following values, according to the method of Zuntz :

	Litres Air per Minute.	*O_2 per Minute.*	*Weight.*	*O_2 per Minute and Kg.*	*Pulse per Minute.*	*Respirations per Minute.*
		C.c.		C.c.		
Non-pregnant period ..	7·10	302	108·4	2·79	72	13
Pregnancy :						
3rd month	7·88	320	111·4	2·88	66	10
4th ,, ...	7·88	325	111·3	2·92	84	13
5th ,, ...	8·38	340	110·7	3·16	84	15
6th ,, ...	9·15	349	110·9	3·14	78	15
7th ,, ...	9·42	348	112·0	3·10	90	15
8th ,, ...	9·26	363	113·5	3·20	90	16
9th ,, ...	9·78	383	115·1	3·33	84	13

The table shows that already in the third month there is a perceptibly increased consumption of oxygen, and in the later months the amount is gradually augmented up to the termination of the pregnancy.

The increase in the consumption of O_2 in the ninth month amounted to 80 c.c., or 25 per cent. of the normal. Of this quantity about 15 to 20 c.c. arose from the increased ventilation and cardiac work. At the most, 10 c.c. of O_2[1] were considered by the author to result from the metabolism and development of the fœtus. The remainder—over 50 c.c. of oxygen—must be due to the increased metabolism in the maternal tissues. Here also come into consideration the organs of the body other than the sexual organs which are directly concerned in the pregnancy. In spite of the similar course of the whole series, and the excellent agreement of the figures relating to the individual months, the author has misgivings as to the general applicability of the results, as he found no distinct increase of the gaseous exchange per kilogramme in two other women in the ninth and tenth months. Franz Müller also noticed no rise up to the fifth month in a series of investigations which was quite as well applied, and certainly as methodically carried out, as that of Magnus-Levy (6).

According to these few investigations one thing can be maintained—namely, that the absolute metabolism during pregnancy does not in any case sink, but rather rises somewhat with the progressive increase of weight in pregnancy. The increase of the gaseous exchange is at least parallel to the increase of weight, the metabolism per kilogramme thus remaining closely similar (5).

From the raising of the respiratory quotient in gravid rats (from 0·70 to 0·80 in the normal to 0·85 to 0·9 to 1·0), Oddi and Vicarelli concluded "that the carbohydrate combustion preponderated, while the nitrogenous material was applied to the elaboration of the fœtus"—that is, the combustion in the maternal organism was thus partially withheld (6). That is not accurate in its general aspect. Again, in the latter months of pregnancy, only a moderate part of the nitrogen of the food is stored up in the tissues of the embryo and of the mother. In the experiments of Hagemann and Jägerroos, who studied the individual periods of pregnancy separately, the retention usually reached as high as 10 to 15 per cent. (an average also of the experiments of Zacharjewsky), but 20 to 25 per cent. was recorded in certain individuals. If, with mixed diet, in which the protein still constitutes only a proportionately small part, 20 per cent. of it becomes spared from oxidation and replaced by carbohydrate, then the respiratory quotient rises at the most about 0·01 to 0·02. The respiratory quotient in pregnancy also becomes essentially ruled by the same conditions as in the non-pregnant state—that is, from the mixture of individual food-stuffs in the food. Thus it will be high if the food contains an excess of carbohydrate, upon which the organism chiefly exists, and still higher when fat is formed from the carbohydrates. That may possibly have been the case with the animals experimented upon by Oddi and Vicarelli. Magnus-Levy found in his pregnant cases during the fasting condition proportionately high values of the respiratory quotient. But these figures only demonstrate that from the last food a certain amount of carbohydrate was retained in the body, which, ten to twelve hours after the last meal, could, to a greater extent than is generally understood, play a part in metabolic exchanges. As on certain days of his series of experiments the supply of food was markedly limited on special grounds, the respiratory quotient sank directly. Through a removal of the materials entering into oxidation the respiratory quotient could certainly alter at the same time. Thus if the carbohydrate after ingestion, instead of being directly consumed, be partly set aside, and first oxidized in the later hours of the day, its combustion would then be distributed equally over the day, as it usually is. But in the course of twenty-four hours an adjustment must take place. It is not possible that pregnancy can otherwise alter the respiratory quotient, which, as in other conditions, is dependent upon the food taken.

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[1] According to experiments on the metabolism in incubated hen's eggs and the guinea-pig embryo (Bohr and Hasselbach). The interesting results of the investigations on the metabolism of the fœtus cannot be repeated on account of the limited space. I therefore refer to the list of literature, No. 17.

No investigations have as yet been made on the exchange of energy in the puerperium and during lactation.

(*d*) Influence of Pregnancy on the Blood.

The alterations of the blood in pregnancy (number of the cells, percentage of hæmoglobin, iron) are for the most part pathological when marked deviations appear. The influence of pregnancy itself cannot yet be accurately estimated, although it tends rather to an increase than to a diminution of the red-blood cells and the hæmoglobin (7).

Blumreich, using Loewy's method, found that the alkalinity of the blood was increased throughout the normal pregnancy of the rabbit and man (8).

(e) The Urine during Pregnancy, etc.[1]

Urea, Uric Acid, etc.—For an explanation of eclampsia as an auto-intoxication one might take into consideration the alleged appearance of imperfect combustion of protein in normal pregnancy. But the investigations of Valdagni, Zacharjewsky, and Schrader (9) show that the urea accounts for 80 to 90 per cent. of the total nitrogen in healthy women during pregnancy and the puerperium, the same amount as is normally excreted. Again, the quantity of the neutral sulphur does not, as a rule, vary in the urine of gravid women, any alterations being only slight [Schrader].

In eclampsia, Zweifel (9) observed a marked increase of the neutral sulphur in many instances, and, just like Valdigni before him, a diminution of the relative amount of urea nitrogen to 70 or 60 per cent. of the total nitrogen (calculated in urine free from albumin). The nitrogen deficit was not covered by the increased NH_3 percentage, so that the so-called "nitrogen residue" was increased up to 17 per cent. of the total nitrogen.

In pregnancy, and also in the puerperium, Zacharjewsky records a normal excretion of uric acid, 0·5 to 0·6 gramme.

The excretion of ammonia has not yet been investigated in healthy gravid women. From the normal height of the urea figures an essential increase of the ammonia, and therefore the existence of a more marked acidosis, appears quite improbable. In eclampsia the ammonia-nitrogen frequently rose to 10 to 15 per cent. [Zweifel], certainly in consequence of primary acidosis; in the urine lactic acid was present.

Zweifel's numerous and very careful investigations demonstrate an alteration in the final elaboration of the protein bodies and the presence of organic acids, yet these disturbances may be regarded rather as a result than as the cause of the spasms. The percentage of urea and ammonia in the blood was not raised in eclampsia [Zweifel].

The albuminuria in pregnancy and in the puerperium shows nothing characteristic in its relations to metabolism. Its effect on the chemical processes is scarcely to be distinguished from those of analogous renal disturbances (6).

Peptonuria.—The excreted "peptone" [Brücke] consists of deutero-albumoses, just as in most cases of so-called peptonuria. The peptonuria appears first on the second day of the puerperium, and then continues in similar quantities up to the fourth and fifth days. The peptone of the lochia is not the source of the urinary peptone, as it may be present in the urine though absent from the lochia.

Fischel's suggestion that the urinary peptone originates from the involution of the uterine tissue, etc., appears to be confirmed by recent investigations on autolysis in general, and that of the uterus in particular [Langstein, Neubauer (10)]. The peptonuria in the puerperium may be compared with that during resolution in pneumonia. According to Ehrström, on the other hand, no peptone is present in the urine when the puerperium is free from fever, the febrile conditions being responsible for its occurrence. Peptone is only demonstrable in the lochia when it is purulent, being present only in the leucocytes. Since the introduction of antisepsis and asepsis into midwifery practice peptone is but rarely found (10).

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[1] See also Matthews, A. J. M. S., 1906, Bd. 131.

Acetonuria.—The statement of Vicarelli and Knapp that acetonuria is only present in pregnant women where the fœtus has succumbed, its appearance being, therefore, of diagnostic value, has been contradicted by Stolz (11). With the actual parturition it is not directly concerned [Stolz]. According to our view, it may be indirectly related in so far as one effect of parturition is to use up the glycogen store of the body; the acetonuria in eclamptics may also be referred to this, as Lorenz has observed. The acetonuria of gravid women and puerperæ likewise appears to be only the consequence of the special conditions of nourishment—viz., of the insufficient supply of carbohydrate. It is transient, and almost disappears after adequate feeding. The amount of excretion of the acetone bodies in the urine is very limited, being insufficient to yield the ferric chloride reaction. In any case, further investigations are necessary on this point in order to complete the general conception of acetonuria as described during the last decade (11).

Glycosuria and Lactosuria.—A special " weakness of the carbohydrate metabolism " does not exist in pregnant women. Alimentary glycosuria may perhaps appear somewhat more readily than otherwise. Lanz frequently found sugar in the urine after giving 100 grammes of glucose, but only twice in quantities worth mentioning—namely, more than 2 grammes (12). With ordinary food the reducing power of the urine of the human female in the few weeks preceding delivery is not raised [Zacharjewsky]. It first rises after birth in connection with the secretion of milk. The sugar then excreted is lactose [Blot, Fr. Hofmeister, Kaltenbach (13)]. It generally appears first with the commencement of the milk secretion, but it is only slight in amount unless the milk becomes reabsorbed instead of being excreted. The percentage of lactose in the urine rarely reaches 0·3 to 0·5 per cent. The absolute amount never exceeds 5 to 10 grammes daily. This is not otherwise than probable, since during the first days of the puerperium hardly any more milk-sugar is formed in the breast. Sinety has recently made a valuable contribution as to the origin of the milk-sugar excreted from the mammary gland. After removal of the mammæ in a guinea-pig the lactosuria immediately disappeared. When the same operation is performed prior to delivery, then lactosuria does not appear [Magnus-Levy and Leo Zuntz in the goat (14)]. The statement of v. Noorden and Zuelger that puerperæ sometimes excrete lactose after the administration of grape-sugar is of great interest (15). These workers consider that puerperæ generally consume a part of the absorbed milk-sugar, but that the more readily decomposed glucose " displaces the lactose from oxidation." The first part of this explanation is quite in opposition to the assertion of Fritz Voit that milk-sugar which passes into the body otherwise than through the intestine is again excreted bulk for bulk. Von Noorden's observations might also indicate that the rich supply of glucose (100 grammes and more) increased the formation of milk-sugar (15).

(*f*) The Metabolism of Salts during Pregnancy.

The individual mineral substances have not yet been fully investigated. According to Jägerroos, the metabolism of salts in general, and that of phosphoric acid in particular, runs parallel to that of the nitrogen. The same remark applies to phosphoric acid and to sulphuric acid [Hagemann and ver Eeke]. Harnack and Kleine found that the neutral sulphur was increased up to 50 per cent. in a pregnant bitch. This is rarely the case in pregnant women [Th. Schrader]. The statements of ver Eeke on the behaviour of phosphoric acid in the rabbit do not prove much, as estimations of the phosphoric acid in the fæces were not included ; the statements regarding chlorine are also not verified by figures. The excretion of salts in the human female with reference to the intake has not been determined (16).

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3. Metabolism after Castration.

Two questions here specially claim the interest of the clinician and the physiologist. The fact that a tendency to obesity appears after removal of the sexual glands in animals and man, especially in the female sex, points to the relations of these organs to metabolism. The deposition of fat after the climacteric period and after castration (in 35 to 40 per cent. of the cases) is often referred to a diminished oxidation energy of the tissue cells. A further relation of the sexual glands to metabolism is shown in osteomalacia. The striking improvement of this bone disease after removal of the ovaries corresponds to a distinct retention of the earthy phosphates, whereby the skeletonal tissues regain their former rigidity (1). The diseased ovaries certainly exert a marked influence on the metabolism of phosphorus. Future experiments must determine whether healthy glands possess a similar function.

(*a*) The Energy after Castration.

Experiments on the respiration alone suffice to prove whether the genital glands exert an influence on the processes of oxidation. The available information is arranged in the following table :

Author (2).	*Animal.*	CO_2.	O_2.	*Length of Experiment.*	*Results.*	
Popiel	Rabbits	+	+	(?)	Diminished gaseous exchange	Compared with period prior to castration.
Curatolo and Tarulli	Dogs and Mice	+	(?)	(?)	Diminished gaseous exchange	
Loewy and P. Fr. Richter	Male dog, female dog	+	+	1 hour (Zuntz method)	Diminished gaseous exchange during rest	
Lüthje	Male dog, female dog (2 controls)	+	–	24 hours (Pettenkofer)	No diminution compared with control animals	
L. Zuntz	4 castrated women	+	+	1 hour (Zuntz)	No (or slight) decrease from " rest " exchange	

Here, as in all similar questions, it is necessary to distinguish whether after castration the total daily metabolism sinks in consequence of a " variation of temperament "—that is, in consequence of a greater tendency to bodily repose—or whether the oxidation energy of the resting cell, the " fundamental metabolism," is diminished. In the latter case there is an immediate effect of the sexual glands on the metabolism ; in the former the action is a more remote one.

The marked diminution of the gaseous exchange which Popiel (2) observed in rabbits is probably due to a greater indolence of the castrated animals. Popiel expressly states that the animals were motionless and lazy in contradistinction to the control animals, which were very lively. The same was apparently the case with the animals used by Curatolo and Tarulli.

Lüthje's castrated dog and bitch, on the other hand, did not exhibit any change from their normal energy and movements. The excretion of carbonic acid (measured in twenty-four hours' experiments) was unexpectedly as high as in the control animals.

The following table gives the CO_2 excretion per hour and per kilogramme :

	Castrated Animals. Gms. CO_2.	*Non-castrated Control Animals.* Gms. CO_2.
Male animals, fed	1·098	1·059
Male animals, fasting	0·845	0·832
Female animals, fed	1·049	1·056

While Popiel and Curatolo's (2) animals, as a result of their laziness, became very fat, the fat-content of Lüthje's castrated animals was no greater than that of the controls. The experiments were well designed,[1] and lasted for a considerable time, and identical diets were given to both the animals operated upon and to the controls ; hence a certain importance attaches to Lüthje's experiments, if only for the special case investigated. With man it is certain that in more than half the cases one does not observe increasing indolence or the putting on of fat. The castration of dogs very rarely, or never, leads to the same result as it does with wethers and other animals, with which the farmer can safely reckon on a good result for his feeding.

Loewy and P. Fr. Richter (2) came to conclusions exactly opposite to those of Lüthje. They found diminutions of 10 to 20 per cent.[2] in the consumption of O_2 and the evolution of CO_2 of a castrated dog and bitch while at rest. The dog showed a distinct diminution after ten days, the bitch, however, only after fourteen weeks. These authors are pupils of Zuntz, and cannot be accused of having designed their experiments imperfectly. But one has to consider whether the lessening of the gaseous metabolism observed after the operation was not referable to the more complete repose enjoyed by the animals. Such an interpretation may at least be entertained.

Loewy and Richter fed animals upon ovarian and testicular substance, and also injected spermine subcutaneously, and obtained highly interesting results. Normal animals did not react at all ; a castrated bitch, on the other hand, when fed with ovarian substance showed a greatly increased metabolism—30 to 50 per cent. above the normal values observed before the operation. When the glandular tissue was withheld, the consumption of O_2 sank slowly to the normal during the next three weeks. It is remarkable that the experiments, though unluckily not sufficiently numerous, showed that oöphorine exercised a similar influence over the castrated dog. Spermine and testicular substance had no effect at all upon either of the castrated animals.

It is not so surprising that feeding with the tissue of the germinal glands should have no effect upon sexually intact animals. The added principles are without any special significance for the metabolism or for the other functions of the body. Were this not so, great variations in the gaseous interchanges would be associated with the variable activity of the sexual functions in man, for it is in man that the variations in this activity reach their highest known development. But we know nothing on this point. Yet it is wonderful, even barely intelligible, that the introduction of ovarian tissue into the castrated dog should increase its metabolism, while testicular substance remained without any action. The testicular function has been abolished, and is compensated for by ovarian extracts, not by the supply of the substances that the animal's body lacks. One might almost call this an instance of "contrary sexualism."[1] But no final decision can be reached here until these experiments have been repeatedly confirmed (2).[2]

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[1] Taking two dogs and two bitches of the same litter, he brought them up in the same way, castrating one dog and one bitch when sexual maturity was first reached. The other two were used as controls. The experiments extended over two years.

[2] Determinations bv Zuntz's method, lasting for half to one hour.

The physician is naturally only convinced by experiments made upon human beings. Leo Zuntz (2) investigated the gaseous metabolism during repose in four women whose ovaries had been removed, and found that it lay within the limits of the normal; none of them had grown fat after the operation. In one of them the metabolism was a little lessened. No investigations have been made upon women who have grown stout after the operation. Hence, for the time being, it is only possible to quote from the very numerous examinations that have been made into the metabolism and gaseous exchanges of persons who are naturally obese. In these the gaseous interchanges have never yet been found to have suffered a diminution. This being so, we must at present regard any corpulence due to castration as in no way different from spontaneous adiposity—at any rate, in the great majority of cases. Fat accumulates because less bodily work is done while the food is taken in augmented quantity, and not because the O_2 consumption of the cells is diminished while they are in repose. Reference should be made to the section on Obesity.

The development of sexual maturity is not indicated by an increase of the metabolism during repose in boys and girls [Magnus-Levy and E. Falk (2)]. The diminution in metabolism that marks old age appears later than the cessation of sexual activity, although this is a point that has not been adequately gone into. Extended experiments made upon the same women both before and after the menopause, and up to old age, are necessary before the matter can be settled. At any rate, the germinal glands do not exercise so great and direct an influence upon the development of heat as does the thyroid gland (2).

(*b*) The Economy of the Protein after Castration.

But few of the modern authors on this subject are accessible for reference [Lüthje, Fr. N. Schulz and O. Falk, and S. Neumann and Vas (3)].

Lüthje's long series of observations never recorded any change in the protein metabolism after castration; the shorter experiments of the investigators at Jena and at Budapesth indicate no more than a trifling increase in the urinary nitrogen. Similar results were obtained by Curatolo and Tarulli, by Mossé and Oulié. Pinzani noted a diminution in the nitrogen of the urine and fæces. Repreff and Popiel remarked an increase in the nitrogen excreted, although, in Popiel's case, less food was being taken, and there may have been an inanitional loss of nitrogen (3). But the reliable results first quoted are unanimous, and no doubt are

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[1] One might easily imagine that the substance of the male germinal glands would act just as that of the female germinal tissue does. The negative results given above perhaps depend upon this: that the active principle of the testis was destroyed, either during preparation or else during digestion.

[2] Leo Zuntz tells me that some years later he again gave Loewy and Richter's castrated bitch oöphorine tabloids, and that he could only observe an insignificant increase in the O_2 intake.

Year.	*Author.*	*Animal.*	*Diet.*	*Nitrogen Analysis.*			*Results in Castrated Animals.*	*Remarks.*	*Investigations before Castration.*	*Investigations after Castration.*
				Food.	Fæces.	Urine.				
1891	Repreff	Rabbit	(?)	(?)	(?)	(?)	Increase N	—	(?)	(?)
1895	Curatolo and Tarulli	3 castrated bitches	Meat and bread	–	–	+	No change	—	Yes	Some months
1897	Popiel	Castrated rabbit	(?)	+	+	+	Increase N	Food intake diminished after castration (4 controls)	(?)	2, 3, and 4 months after castration
1899	Schulz and Falk	2 castrated bitches	Meat and fat	–	–	+	Slight increase of urine N	—	Yes	1 to 10 days and 7 weeks after castration
1899	Pinzani	1 bitch	Milk and bread	–	+	+	Urine and fæces N diminished	—	(?)	(?)
1899	Mossé and Oulié	3 bitches	Meat	–	–	+	Unchanged	—	Yes	(?)
1902	Lüthje	1 castrated dog and 1 bitch	Meat and rice	+	+	+	No change (N equilibrium)	1 male and 1 female control	Yes	For several months
1902	Neumann and Vas	1 bitch	Meat and biscuit	+	+	+	Slight increased excretion N	—	Yes	5 to 8 days after castration and later

correct. For the case of human beings, Matthes' investigations upon ovariotomized women are the only results available. They are valueless in this regard, seeing that the food taken is not recorded and was not analyzed (3).

(c) The Influence of Castration on the Metabolism of Phosphorus.

This might be investigated in two ways. Either the P_2O_5 balance-sheet might be obtained by daily examination of the metabolism, or the entire tissues might be analyzed after castration. Both methods have been employed, yielding very contradictory results. The age at which the operation is performed is of importance; the accruing results will differ according as it is done either before puberty, or in the first half of sexual maturity, or in its second half. Transient disturbances may be observed to vanish later, and the time at which the observations are made may influence the results obtained.

It might be expected *a priori* that castration would but slightly affect the metabolism of the bones. Gelded animals are not known to suffer particularly from weakness of the bones. Removal of the organs when they are diseased, however, leads to quite other results, as is elsewhere recorded in this volume.

The following table shows the experimental results obtained in healthy animals:

Author.	*Animal.*	*P_2O_5.*			*Results.*
		Food.	Fæces.	Urine.	
Curatolo and Tarulli	3 bitches	–	–	+	Urinary P_2O_5—large decrease
Pinzani	1 bitch	–	–	+	Urinary P_2O_5—decreased
Mossé and Oulié	3 bitches	–	–	+	Urinary P_2O_5—slight increase
Falk and Schulz	2 bitches	+	+	+	P_2O_5 equilibrium !
Lüthje	1 dog, 1 bitch	+	+	+	P_2O_5 not changed after the operation, and contrary to the controls. At all times a negative balance !
Neumann and Vas	1 bitch	+	+	+	P_2O_5 equilibrium as before the operation; CaO balance also the same

P_2O_5 balance-sheets have been worked out by various authors, for bitches in every case. Only Lüthje, O. Falk, and S. Neumann (4) determined the P_2O_5 in the food as well as that in the urine and fæces. When a diet of meat only is given, the want of analyses of the fæces is not so very important; the dog excretes only 10 per cent. of its P_2O_5 in the motions. But as Curatolo and Pinzani gave their animals bread and milk, their figures are useless, for with such a diet the fæcal P_2O_5 is considerable—and, what is more important, variable—in amount. The colossal retention of P_2O_5 calculated by Curatolo and Tarulli—169 grammes in 211 days—has been very properly discredited on all hands; it would have increased the animal's skeleton by about 100 per cent. The work of Lüthje, O. Falk, and S. Neumann next led to the conclusion that the removal of normal germinal glands had no influence upon the phosphorus-metabolism. The experiments of the two latter authors were too short to settle the question. Lüthje found, curiously enough, that the P_2O_5 balance-sheet in all the six series of observations, before and after castration and in the whole animals, gave negative balances, while the nitrogen balance-sheets, with one exception, showed a retention of nitrogen.[1]

Determining the P_2O_5 in the bodies of the animals after death, distinct differences might be expected between gelded and whole animals, according to Lüthje's views. Our own calculations lead to quite other conclusions. The P_2O_5 in the dried skeletons was as follows:

	Gelded Animal.	*Whole Animal.*
Male	About 5·4 per cent.	About 5·4 per cent.
Female	„ 6·9 „	„ 8·9 „

Quite apart from the differences between the whole and the castrated animals, the low values for the P_2O_5 in the skeletons of each of them are most striking. Values of this average size have never yet been recorded for grown animals by any other writer, and Lüthje's animals were full grown. The lowest values to be found in the hundreds of careful bone-analyses recorded are over 13 per cent. Some error must have crept into the preparation of the skeleton for analysis, making it impossible to attach any kind of importance to Lüthje's figures.

Working in Salkowski's laboratory, F. Heymann (4) found a considerable diminution in the total P_2O_5 contained in the body, and particularly in that of the bones, in ovariotomized rats. The loss was greater the longer the time that intervened between the operation and death. This fact does not explain the observation that in osteomalacia the bones lose their consistency if the ovaries become diseased, and that cure of the ovarian lesions puts a stop to that process.

It only remains to record these very contradictory experimental data, leaving their explanation to the future (3). At the present time it seems impossible to disentangle from them anything that might make the process of osteomalacia more intelligible.

(*d*) Feeding with Ovarian Substance, and its Effect upon the Metabolism.

The administration of ovarian tissue has not led to any regular results. Neumann and Vas (5) record losses of N, P_2O_5, and CaO consequent upon the injection of large amounts of glycerine extract of the ovary *sub cutem*; they worked out careful balance-sheets. Feeding with twenty-five tabloids produced but little loss.

The following investigations deal with gelded animals: A. Loewy and also Neumann found the nitrogen balance-sheet unchanged;

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[1] The P_2O_5 lost in the six series varied from 2·3 to 5·8 grammes. The gain of nitrogen in five series was from 7·1 to 22·6 grammes.

Neumann observed slight losses of P_2O_5 and CaO, mainly due to increased excretion in the fæces. Curatolo and Mossé disregarded the fæces; the former observed an increase, the latter a decrease, in the urinary P_2O_5, and both results may be rejected. So may Matthes' work, for he did not analyze the food given. The same objection may be made to Senator's investigation of a case of osteomalacia. Senator (5) also found a distinct rise in the urinary nitrogen and in the urinary and fæcal CaO and P_2O_5, while the diet remained apparently the same.

(*e*) The Influence of Castration on the Blood.

Pinzani records an increase in the hæmoglobin and red cells of bitches after ovariotomy. Lüthje gives detailed tables, finding no such change here; the white cells and the iron remained unaltered in value for months after the operation. Breuer and Seiler, on the other hand, made numerous thorough investigations upon bitches castrated soon after they became sexually mature; they regularly found marked diminutions in the hæmoglobin and the red cells, which only returned to their normal values after the lapse of several months. Thus they proved that the ovaries influence the formation of the blood. But it is not possible to apply their discovery to the discussion of chlorosis, because the hæmoglobin and red cells diminished *pari passu* in their animals, and this does not occur in the "green sickness" of human beings.

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E.—THE BEHAVIOUR AND RÔLE OF WATER IN THE METABOLISM.

1. The Intake of Water.

Water in the Food and the Water formed by Oxidation.

The amount of water taken in the food and drink varies according to the position, life, habits, and habitat of the individual. The variations are so wide that it is quite unjustifiable to set down any average values, but the following figures give at any rate an idea of the amount of water taken on the mixed diet under comfortable circumstances: Forster calculated that 2,300 to 3,500 c.c. of fluid were taken at Munich, including 1 to 2 litres of beer. Atwater and Benedict (1) found the average of forty-nine days of repose to be 2,290 c.c. (= 880 to 2,440 c.c.), the mean of sixty-six working days being 3,700 c.c. (= 2,225 to 4,450 c.c.) of water.

In addition to the fluid drunk the body has at its disposal the "oxidation water" resulting from the combustion of the hydrogen in the food. The amount of this varies but little, depending less upon the nature of the foods oxidized than upon their quantity—*i.e.*, upon the absolute extent of the metabolism. The following easily understood table shows this:

	Contain Gms. H.	*Yield Gms. H_2O.*	*Yield Calories.*	*100 Calories Yield Gms. H_2O.*	
100 grammes fat	11·9	107·1	9,461	11·3	13·3
100 grammes starch ..	6·78	55·5	4,181	13·3	
100 grammes protein ..	4·59	41·3	4,442	9·3	
100 grammes alcohol ..	13·04	117·4	6,981	16·8	

Thus for each 100 calories developed, the different kinds of food produce more or less the same amounts of water—approximately 11·3 grammes. On a mixed diet, where half the potential energy is derived from the carbohydrate, one-sixth from the protein, and the remaining third from the fat, each 100 calories correspond to about 12 grammes of water, so that—

From	2,000	2,500	3,000	3,500	4,000 calories.
About	240	300	360	420	480 "oxidation" water.

It is only when the quantity of alcohol imbibed becomes very large that relatively more water is produced by oxidation. The approximate figures just stated agree fairly well with the quantities determined experimentally. Thus Voit (1) found that—

During starvation	32 gm. H=288 H_2O, with an exchange of about 2,300 calories.
With average diet and light work	40 gm. H=360 H_2O, with an exchange of about 2,600 to 2,800 calories.
With hard work	52 gm. H=468 H_2O, with an exchange of about 3,600 calories.

Atwater and Benedict observed—

During rest	30 gm. H=270 H_2O, with an exchange of about 2,209 calories.
During hard work	50 gm. H=451 H_2O, with an exchange of about 3,630 calories.

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2. The Methods by which Water is excreted.

Evaporation.

Little water is lost in the fæces, relatively speaking—from 60 to 120 grammes a day, on an average diet and with normal evacuations. Should the diet be such as to increase their bulk, the quantity of water increases. On a strictly vegetarian diet consisting only of cereals and fruit it may reach 300 grammes.

Other things being equal, the quantity of the urine varies inversely with the amount of the perspiration. The surplus left by the skin is excreted by the kidneys. Reference only will be made here to the habitually small amount of urine passed by vegetarians—300 to 1,000 c.c., which undoubtedly stands in close relation to the small amount of solids it contains. This diminution in volume is established quickly, and occurs as soon as the transition is made from a meat diet to the vegetable foods poor in nitrogen [Voit, Peschel, and others (1)].

(*a*) The Daily Evaporation during Repose and during Work.

The evaporation from skin and lungs varies widely in any individual on a fixed diet in accordance with atmospheric conditions. Pettenkofer and Voit (2) give the mean as 931 grammes (680 to 1,200 grammes) in the twenty-four hours. Atwater and Benedict record similar variations; the mean of their forty-nine investigations on four persons is 935 grammes. These figures hold good for quiet occupations in well-ventilated rooms at comfortable temperatures and degrees of humidity. Only a little less water vapour is given off during starvation than on a full diet.

But during bodily work the quantity increases greatly. The figures given below were all determined in the respiratory chamber :

	Perspiration Water in 24 Hours.		*Energy Exchange.*		
	Rest (Average Grammes).	Work (Average Grammes).	Rest (Calories).	Work (Calories).	
Uhrmacher ..	931	1,727	2,300–2,800	3,600–3,800	P. Voit (2).
E. O.	977	2,275	2,278	3,829	Atwater and Benedict(2).
A. W. S. ..	859	—	2,279	—	
J. F. S. ..	830	1,670	2,136	3,540	
J. C. W. ..	835	3,255	2,397	5,120	
J. C. W. (hunger)	869	—	2,187	—	
J. C W. (hard work, 16 hours)	—	7,381	—	9,134	

Speaking generally, the amount of water vaporized increases with the amount of work done and heat developed, other things being equal. With moderate amounts of work 1·5 to 2·5 litres are evaporated ; with heavy work, over 3 litres ; and as much as 7·5 litres with the extremely hard work of the lowest row of figures. The wide variations here are obvious. When equally large amounts of work are done in the open air the evaporation must be increased. Zuntz and Schumburg found it was from 1,900 to 3,200 c.c. in students walking 27 kilometres in seven hours—five of walking and two of repose (2).

(*b*) The Hourly Evaporation during Repose and during Work.

During quiet occupations indoors, under the conditions stated in the last section, the amounts of water evaporated during the separate hours of the day are fairly constant. The hourly average determined by Atwater and Benedict (4) in all their experiments upon four individuals worked out at 38·9 grammes. The minimum was 31 grammes in one person, the maximum was 41 grammes in another ; the maximum and minimum values for each individual lay near one another. The smallest value for the twenty-four hours was found at night, when the body rests, and was only 10 per cent. smaller than the mean hourly value by day.

When work is being done, the evaporation is greatest when the labour is heaviest. Thus J. C. W., who did the hardest work, evaporated 160 to 350 grammes an hour, averaging 275 grammes ; more than 400 grammes were lost in the hour when the most violent work of all was performed. In the open air the amount evaporated is relatively greater even when the work is not hard. Thus, 300 to 400 grammes and more [Nehring] may be lost when 20 to 30 kilogrammes are carried during marching. Similar figures may be looked for on mountaineering expeditions. Oertel (4) states that even the slow ascent of hills may cause 200 to 300 grammes of water to be lost in the hour.

(*c*) The Evaporation from the Skin and from the Lungs.

Rubner (5) measured the evaporation from the lungs. When the temperature and relative humidity of the air were about the average, he noted that 17 grammes were lost during repose, 19 grammes during deep breathing, 28 grammes during reading aloud, and 37 grammes during singing, per hour. The amount given off depends upon the degree of ventilation obtaining, for during repose, at any rate, the expired air is saturated with moisture. Rubner holds that this is not the case for the much increased pulmonary ventilation of hard work. Calculating from the physical data, the 15 cubic metres of air expired daily by persons at rest should evaporate 400 to 500 grammes of water [J. Rosenthal (15)]. Respiration deepens when work is done, and then this quantity may well increase 50 per cent. or more (5).

A portion of the vapour given off by the skin always comes from the sweat, even when the excretion of that fluid remains imperceptible to the eye. NaCl can always be detected upon the underclothes under these conditions [E. Cramer]. For the rest, the secretion of sweat covers only a part of the water evaporated, and a percutaneous evaporation must also take place [E. Cramer, Schwenkenbecher (6)].

In all, 930 grammes of water are lost daily during repose indoors. About 550 grammes, or 60 per cent., come from the skin, the remaining 400 grammes being given off by the lungs. These figures agree with the direct measurements of the water given off from the surface of the body made by Schierbeck and by Willebrandt (6). The increased loss observed during work, or when the temperature of the body rises, comes mainly from the skin; the evaporation from the surface of the respiratory tract varies within comparatively narrow limits.

(*d*) Climate and the Evaporation of Water.

The numerous researches of Rubner's pupils provide very accurate information upon this point. The temperature of the air is the most important variant in climate. The evaporation of water from the body is least in temperate climates; it is greater at low temperatures, and is much increased at high temperatures [Rubner (7)]. The figures in the following tables are all calculated for periods of one hour, unless it is otherwise stated:

Temperature (Cent.) ..	2°	10-15°	15-20°	20-25°	25-30°	30-35°	35-40°
H_2O lost per hour ..	37	28	19	23	43	84	112 grammes

The values found for this man were distinctly lower than those of the other persons examined in the same laboratory.

The next most important point is the relative humidity of the atmosphere. When the value of this was very high, a lightly-clad man at rest lost the following amounts of water [Rubner and Lewaschew (7)]:

Temperature (Cent.)	15°	20·4°	25·3°	28·9°	
In dry air (5 to 8 per cent. moisture) ..	36·3	54·1	75·5	105	grammes H_2O.
In damp air (81 to 89 per cent. moisture)	9·0	15·3	23·9	—	

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Air very nearly saturated with moisture can only take up a little more water-vapour. Hence the body loses less water in damp than in dry air.

The temperature and relative humidity of the atmosphere are always important here; the other circumstances are less so. At average temperatures the movements of the air produced by a moderately strong wind diminish the loss of water to a greater or less degree [Wolpert (8)]. This is, in part, because more heat is being lost by convection, so that the amount of heat to be lost by the evaporation of water is lessened. But if heavy work is being done, increase in the velocity of the wind ensures a more rapid evaporation and loss of heat, diminishing thereby the perspiration and the excretion of liquid sweat [Zuntz and Schumburg, Zuntz (8)].

Exposure to the powerful rays of the sun increases the evaporation greatly, for manifold reasons [Rubner and Cramer (9)]. Increase of the subcutaneous fat lessens the water lost at low temperatures, but increases the excretion till it flows away in streams at high temperatures [Wolpert (10)].

Individuals of different races clothed in the same way and at the same temperature lose equal amounts of water. Rubner (11) has proved this definitely by numerous and varied experiments made upon Europeans and negroes.

To consider next the loss of water when work is done under various climatic conditions. Light bodily work done indoors in temperate climates increases the evaporation only a little. Wolpert (12A) observed the loss of 29 to 56 grammes during repose to increase to 56 to 61 grammes during light industrial labour. Moderate ergostatic work—5,000 kilogramme-metres in an hour—produced only a slight augmentation up to 50 grammes of water. Work at the rate of 15,000 kilogramme-metres—no great effort for a sturdy workman—raised the loss of water much more, particularly at high temperatures, 150 to 200 grammes being lost in a dry atmosphere [Wolpert (12B)].

	Temperature.	*Rest.*	*Work (5,000 M.-kg.).*	*Work (15,000 M.-kg.).*
	° C.	Gms. H_2O.	Gms. H_2O.	Gms. H_2O.
Dry air (30 per cent. relative moisture)	15	50	55	55
	20	60	60	70
	25	65	105	150
	30	100	145	220
	35	160	170	—
Damp air (60 per cent. relative moisture)	15	20	25	25
	20	25	50	—
	25	35	85	—
	30	65	110	—

As the mean of a number of experiments upon himself, Wolpert (12C) found that with variable conditions of humidity and temperature he lost 42 grammes at rest, 115 grammes while doing 15,000 kilogramme-metres of work, in the hour.

(*e*) The Influence of the Nutrition upon the Cutaneous Evaporation.

The consumption of much water increases the amount of urine, but leaves the evaporation unchanged. Latschtschenko (13) drank 250 c.c. of water every half-hour, 2 litres in all; the water lost by evaporation during the five hours remained unaltered whether the air was cool or quite warm. This holds good for persons at rest; it might be quite otherwise with men at work or on the march, particularly if they were untrained and perspired more freely than was necessary.

Alcohol imbibed freely—250 grammes of Nordhausen brandy, containing 92 grammes of alcohol—raised the excretion of sweat in a number of Rubner's (14) experiments whether the temperature of the air was high or low. The whole increase—7·9 to 14 grammes—must be set down to the primary vaso-dilatation in the skin.

The taking of solid food can sometimes lead also to an upset of the economy of the fluids and to the increased loss of water. This occurs when overeating occurs, where the liberation of heat after meals is much increased, particularly when the diet is highly nitrogenous [Rubner (15)].

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3. Evaporation and the Regulation of the Temperature of the Body.

The nature and extent of the evaporation are of the highest importance for the regulation of the body heat. The evaporation of 1 litre of water may cost the body some 580 calories. Clinical investigation attacked this subject, and, after making a good beginning, left it with indecent haste, but now, however, begins to look into it once again [Schwenkenbecher, G. Lang (1)]. The regulation of the temperature in the corpulent, in patients with exophthalmic goitre, or in cases of fever at the onset and defervescence, and so on, are of great significance for the proper understanding of the metabolism of these conditions.

From the more recent results[1] Rubner (2) calculates that an 80-kilogramme man, who is doing no particular work—*i.e.*, work in Category I.—divides up his losses of heat at average conditions of temperature and humidity in the following way:

	Calories.	*Per Cent.*	
Warmth from atmosphere (11·6 kg. = 8·3 cb.m.)	35	1·3	4·6
Warmth from food	42	1·5	
External work	51	1·9	
Water evaporation (931 gm.)	558	20·7	
Conduction	833	30·9	74·6
Radiation	1,181	43·7	
	2,700		

It should be observed that the heat lost in the form of external work is commonly *nil*, seeing that the work performed in walking is almost all of it returned to the body in the form of heat. It is only when heavy mechanical labour is performed, or elevations are ascended, etc., that chemical energy is converted into real external work. Perhaps one ought to put the figure for the loss of heat by the evaporation of water a little higher, because Rubner took the amount here from a lighter individual weighing 67 kilogrammes. Atwater and Benedict (2) set down the heat lost by evaporation during repose at 24·5 per cent. of the total.

When work is done, the loss of heat by evaporation grows considerably, but not enough to account for all the excess of heat thus developed. The following table has been made up from Atwater's figures; O. Nehring (3) should be consulted here.

Very heavy work was done here. About 40 per cent. of the heat lost, excluding the energy converted into mechanical work, went to evaporate water. During the actual working period this loss was, of course, still greater; it reached 50 per cent. and more in the experiments done when the temperature, etc., were of average values. In the open air, when the sun is shining and the air warm, 60, 70, or even 80 per cent. of the heat produced may go to evaporate water [Nehring]; these numbers vary, however, in different individuals. (3).

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[1] For the earlier determinations, see J. Rosenthal (2)

	H_2O Evaporation.		*Difference between Work and Rest.*	*Produced Warmth (excluding External Work).*	*Difference of Warmth produced during Work and Rest.*
	Grammes.	Calories.			
			Calories.	Calories.	Calories.
Rest	935	548	—	2,262	—
Hard work	2,848	1,651	+1,103	4,225	1,963
Excessive work ..	7,381	4,281	+3,733	7,832	5,570

The vaporization proceeds still more rapidly when the air is hot and dry, as the repeatedly proven possibility of remaining in hot ovens shows. Loss of heat by conduction or radiation is here impossible, and the temperature of the body must be regulated entirely by evaporation. This condition of affairs begins at 35° to 40° C., when the atmosphere is still. Rubner (4) calculates that the amount of heat got rid of by evaporation is 16·7 per cent. at 15° to 20° C., 30·6 per cent. at 25° to 30° C., and 112 per cent. at 35° to 40° C.

The temperature of the body always rises when the loss of heat proceeds too slowly. The commonest conditions under which this occurs are:

1. Great heat and humidity of the atmosphere.
2. Hot baths.
3. Violent exercise when the temperature is high and the sun shines strongly (= sunstroke).

A rise of 1° in the body temperature of a 70-kilogramme man indicates the retention of about 60 calories, if the specific heat of the body be taken as 0·83.

The way in which the secretion of sweat and the evaporation of water keep the temperature of the body normal is very admirably demonstrated by Tendlau's (5) experiments upon a man with congenital defect of the sweat glands. The man's temperature rose to 40° or 41° C. rapidly when he did heavy manual labour, or after he had sat for some time exposed to the rays of the summer sun. Persons who are defective in this way can only do bodily work in summer if they souse their clothes and body with water at regular short intervals, as Quilford showed was the case with another similar person who worked in the fields. Reference should also be made to Zuntz's interesting remarks upon the inadequate cooling of tracheotomized dogs set to work hard (5).

When the work is not too heavy and the climate is temperate, the production of sweat is so well adapted to the demand for cooling that practically no more water is excreted than can be vaporized at once. But when the heat is not readily got rid of, and particularly if the body has just previously been overheated, the secretion takes place more rapidly; drops of perspiration appear, moisten the skin, and wet the clothes. The regulating mechanism overshoots the mark, and only a part of the sweat secreted serves to cool the body [Schattenfroh (6)]. Zuntz (6) has given a singularly lucid exposition of the hygiene of the excessive sweating that may be observed "on the march."

The Excessive Production of Sweat.

When it happens that the secretion of sweat fails to attain its object and cool the body, as occurs when work is done in hot moist air or in hot baths [Spitta (6)], the perspiration continues to run off in streams so long as the temperature of the body is raised.

In moderately damp still air, fluid sweat first appears at 32° to 34° C. [Schierbeck, Willebrandt, Schwenkenbecher (7)]. If work is being done, it is seen sooner, according to the amount of labour performed and the atmospheric conditions. It is under these circumstances, rather than in repose, that individual variations in the secretion of sweat occurs. The two medical men, Schumburg and Zuntz, under identical conditions, gave off amounts of perspiration differing by 1,000 grammes [Nehring (7)]. In their later pedestrian experiments the insensible perspiration lessened notably, and they "sweated" much less. The "training of the sweat glands," familiar to every tourist, consists in the encouragement of the secretion at the earliest possible moment—that is to say, before the temperature of the body has risen—so as to forestall and prevent the rise. If this is done, no large amounts of excessive sweat appear on the skin, which, accordingly, exhibits only a relatively small quantity of it in the fluid form.

A great many corpulent people distinguish themselves by the possession of such unpractised sweat glands. Their massive adipose deposits lessen the amounts of heat they can lose by conduction and radiation, for they prevent the direct conduction of heat from the interior of the body to its cooled external surface; perhaps, too, in some cases there is also a lack of blood. In this way, though only if the cutaneous circulation is poor, the warming of the skin, and so its loss of heat by conduction and radiation, may be impaired. This improper cooling, on the one hand, and the faulty excessive secretion of sweat on the other, may both be clearly recognised in the following figures collected from the writings of Wolpert and of Brodien and Wolpert (8). Their fat man was quite healthy and capable of doing work. He was bathed in perspiration by the time the temperature reached 28° to 30° C.—*i.e.*, 4° C. lower than the normal. When set to work in a hot atmosphere, he poured out very large quantities of sweat, less than half of which was vaporized.

As an increased evaporation hinders excessive heating of the body, so, contrariwise, does diminution of the evaporation lessen the amount of cooling. But this lessening of the heat loss has its limits. Persons reposing indoors give off about 900 grammes of water vapour, and 30 to 40 per cent. of this comes from the respiratory tract. This loss takes place mainly in obedience to physical conditions, and it can hardly be lessened by the physiological processes of regulation. In case of emergency, only the amount of water given off from the skin can be curtailed. To what extent this can occur has not yet been satisfactorily determined.

	Temperature (° *C.*).	*In Dry Air.*		*In Damp Air.*		
		Evaporated H_2O.	Drops of Sweat.	Evaporated H_2O.	Drops of Sweat.	
Healthy (5,000 m.-kg.)	30	145	0	110	0	Wolpert
	35	170	0	(?)	(?)	
Obese (5,750 m.-kg.)	28–30	170	31	116	62	Brodien and Wolpert
	36–37	186	255	269	266	

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4. The Influence of Changes in the Supply of Water upon the Metabolism.

(a) Increased Input of Water.

(α) *The Protein Metabolism.*

If when the excretion of nitrogen is at a constant level more water is drunk, diuresis occurs, and the urinary nitrogen increases in amount. No increase takes place if no diuresis occurs. It has long been asked whether this increased nitrogenous excretion signifies that more protein is decomposed, or whether it points to nothing more than acceleration of process, by which urea and the extractives are washed away out of the tissues. The question once gave rise to lively discussions.

It seems improbable, *a priori*, that flushing of the system with water should augment the breaking up of so important a substance as protein. Yet this view has been supported by Bischoff, by Forster and Henneberg, and by Voit in particular (1), who was the first to make really trustworthy experiments upon this question. The rise in the excretion of nitrogen was 25 per cent. in his investigations on dogs, a figure much higher than that given by other authorities. It is only in the case of Forster's fasting dog that the urea increased from 12·1 grammes to 22·9 grammes, the urine rising from 200 c.c. to 2,000 c.c.; the increase here was 90 per cent. An increase in the total urinary sulphur was observed at the same time, and Voit holds that this speaks for an increased protein decomposition; it may, however, quite well be attributed to an augmented washing out of sulphur compounds from the tissues, and, in any case, it falls far short of the amount of increase of the nitrogen excretion (1).

The majority of other authors believed that the urinary nitrogen increases because the tissues are more thoroughly washed out and lose their nitrogenous end-products; Bidder and Schmidt, Seegen, A. Fränkel, Salkowski, J. Munk, and J. Mayer may be mentioned here (2). Two facts speak decisively in favour of this view. One is the small extent of the increase; the other, that the augmented nitrogen excretion is only observed during the first few days of the increased consumption of drink [J. Mayer (2)].

Since these early days the latter of the two views has been fully confirmed by careful experiments made upon human beings. Oppenheim drank water at intervals of four hours—2 litres at first, 1 litre later. Only the first draught caused an increase, 3 grammes more nitrogen than usual appearing in the urine of the next four hours; the later draughts did not lead to any increase. In three experiments upon men von Noorden observed increases in the urinary nitrogen twice; the quantities here were only 2·8 grammes and 1·9 grammes of nitrogen during two days. In these cases the fluid taken before the experiments began was only 900 to 1,000 grammes of H_2O a day, and the relatively large addition of 1 or 2 litres caused this transient increase in the urinary nitrogen. But in the third experiment, where 2,300 c.c. of water had been taken daily, the further addition of 1,500 c.c. made no difference to the nitrogenous balance-sheet. Hence von Noorden is led to advise that water should be exhibited freely before experiments upon metabolism are begun, so that changes in the water consumed may then no longer influence the excretion of nitrogen.

The best investigations are those of R. O. Neumann (3). Below I have tabulated the chief results of his twenty-four-day experiments, which were conducted upon himself in an ideal manner, and upon a constant diet.

Period.	*H_2O in Drinks.*	*Nitrogen Balance.*									*Total for Entire Period.*
		Day—									
		1st.	2nd.	3rd.	4th.	5th.	6th.	7th.	8th.	9th.	
1	970	+0·42	+0·19	+0·16	−0·06	—	—	—	—	—	+0·4
2	3,000–3,900	−3·8	−2·4	−0·1	—	—	—	—	—	—	−6·3
3	600–900	+3·35	+1·92	+0·78	—	—	—	—	—	—	+6·1
4	3,100–3,700	−3·16	−1·51	+0·59	+0·51	−0·23	+0·19	+0·59	+1·0	+1·23	−0·89
5	700–1,700	+2·91	+0·72	+0·42	+0·88	—	—	—	—	—	4·9

In Periods 2 and 4 Neumann's consumption of drink rose directly from 600-1,000 c.c. to 3,000 c.c. of water. The urinary nitrogen was increased only upon the first two days. On and after the third and fourth days he remained in nitrogenous equilibrium, although he continued to drink abnormally large amounts of water. The particular value of his researches lies in the fact that he continued to work out the nitrogen balance-sheet. When he returned to the small consumption of fluid (Period 3), or after he had flushed out his system for a long time (Period 4), the initial loss of nitrogen was fully made up for by the retention of corresponding amounts of nitrogenous substances. Thus, for adult healthy man the question has been answered once and for all. It all turns on the flushing of nitrogenous end-products out of the system; there is no abnormal breaking up of protein.

In Neumann's experiments, the amount first washed out and then retained was about 6 grammes of nitrogen. One might be tempted to regard this quantity as the maximum "excess of extractives loosely retained in the system," and to base other calculations upon it as such in other investigations of the metabolism. Were this justifiable, one would be able to set down any further excess of nitrogen lost with some certainty to the decomposition of protein. But this view is not justifiable, since such consumption of water produces no more than a mechanical flushing of the tissues. Under different circumstances, it is quite possible that perhaps larger amounts of extractives might leave the tissues; yet it is most important that conclusions drawn from the action of the healthy body should not be applied to diseased tissues. And there is one thing that these experiments bring out very clearly, and that is the tenacity with which the organism holds on to its extractives. With but few exceptions, these bodies should not be regarded as the valueless decomposition products destined for excretion only. They must rather have definite functions—of which we know nothing for the most part—to perform in the economy of the body.

The influence of water-drinking upon the excretion of salts has, unfortunately, been somewhat neglected in the recent experiments made with such care upon man.

(β) *The Consumption of Energy.*

We have no certain knowledge of the effect of protracted considerable flushing of the system with water upon the development of heat. The observations already recorded do not justify the supposition that the inordinate consumption of fluid leads directly to an increase in the gaseous exchanges. In Latschtschenko's experiments (4) 2 litres were taken in four hours; all this fluid was excreted within five hours, and the CO_2 excretion during this period was not augmented. It has not been determined whether any secondary effect is produced should the conditions last longer, but it is improbable that this would occur. Most authorities who have investigated diabetes mellitus or insipidus, where the urine is much increased, have found that the metabolism remains unchanged. The warming up of the large volume of water drunk lays a certain tax[1] upon the heat produced by the body; but perhaps less heat is given off from the skin under these circumstances, so that the loss is compensated. In a certain sense, one might suppose that the dissipation of heat is transferred from the external surface of the body to the mucous membrane of the alimentary tract; and as there is no question of an abnormal loss of heat here, but only of a transference of its dissipation from one organ tissue to another, there is no good reason why the body should use up more energy in heating the large quantities of water here concerned.

Breeders find [Henneberg (8)] that nutrition is impaired if much water is drunk. But it has not been made out whether the putting on of flesh or of fat suffers. One could only speak of increased oxidation here if the latter were the case; still, the facts certainly admit of a variety of explanations.

(b) Lessening or Withdrawal of the Supply of Water.

In contradistinction to the experiments with the increased supply of water, those where it has been lessened are of recent date. They were suggested by the writings of Oertel and Schweninger. Landauer, Straub, and Spiegler investigated the conditions in dogs, Dennig and H. Salomon those in men, and the results obtained agree in all essentials (5). The experiments made upon man led to the following conclusions.

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[1] Von Noorden (4) calculates the cost of warming up the 8 litres of water drunk by a boy of 24 kilogrammes with diabetes insipidus at 150 calories.

(a) *The Excretion of Water.*

When fluid is completely withdrawn from the diet, the subject of the experiment has only from 700 to 800 c.c. of water at his disposal per diem, 500 c.c. coming from his food, 200 to 300 c.c. from his oxidative processes.[1] His excretion of urine commonly sinks to from 500 to 300 c.c. [Dennig], or even to 200 c.c. [Bartels (5)]. Only in special instances—the corpulent, for example, or on the continuous repetition of thirst cures—does this diminution of the urine become less marked [Dennig (5)]. The calculated perspiration, which is not quite the same as the water vapour given off by skin and lungs, diminishes at the same time. From about 1,000 grammes it falls to a few hundred grammes, remaining low for the first two days after the free consumption of water has begun again. That this shrinking evaporation mainly depends upon the skin there is no doubt; the lungs are much less, or not at all, concerned. Hence dogs, possessing no sweat glands, exhibit a much smaller diminution here than men do [Straub]. Dennig investigated a thin patient, and found that the loss of water by evaporation was much less on the immediate repetition of a thirst cure than it was during the first application of the same; this, of course, only holds good on the supposition that the patient had not access to an illicit supply of water. The evaporation falls on the first day, and then remains at the same level; the organism adapts itself, and thereafter deals far more economically with its fluid (5).

The weight lost during a "crushed grain cure" lasting five to seven days amounts to 3, 4, or even 5 kilogrammes. From 2 to 3½ litres of water are lost, equivalent to 6 to 8 per cent. of the fluid in the body; with dogs the loss is relatively greater, up to 10 per cent. The water thus excreted arises only to a small extent from the breaking down of tissue substance; by far the greater part of it is derived from inspissation of the tissue juices.

(β) *The "Drying" of the Tissues.*

The specific gravity of the blood has only been determined in anæmic persons, not in the healthy; that of the blood-serum rises 2, 3, or in special cases even 6, parts in a thousand, while its residue left on drying increases 0·5 per cent. or more [Jürgensen, Dennig (5)]. Thus, the dried residue of the blood-serum in a case of Dennig's was 9·4 per cent. before a thirst cure lasting several days began, and 10·86 per cent. after it was concluded. Assuming that the blood became concentrated from loss of water only, and not also because it took up solids (possibly mineral matter (?), etc.) from the tissues,[2] then 100 c.c. of serum containing 9·4 grammes of residue and 90·6 c.c. of H_2O thickened into 86·6 c.c., also containing 9·4 grammes of residue on drying. Thus, 100 c.c. of serum lost 13·4 grammes of water. In another case of Dennig's the serum left 8·9 per cent. of residue on drying before the thirst cure, and 11·6 per cent. after it; in this case 100 parts of serum must have lost 23·3 parts of water (?). The red-cell count often rises by 500,000 to 700,000, the hæmoglobin by 1 to 2 per cent., but rarely more, although in a particular case of Dennig's it rose from 13·96 to 16·7 per cent.[1]

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[1] Dennig's evaluation of the oxidation water contains very considerable errors.

[2] Further analyses are lacking, so that the question cannot be settled.

Straub found that the dried residue of the blood rose from 22·03 per cent. to 24·49 per cent. in dogs; this corresponds to the loss of 10 grammes of water from 100 c.c. of blood. In the same way, five days of thirst increased the fat-free dried residue and the fat of a dog's muscle from the normal 20 per cent. and 2 per cent. to 25·5 per cent. and 2·5 per cent. respectively [Straub (5)]. Here I calculate that 100 grammes of the normal muscular tissue lost 21·4 grammes of water, or over a quarter of the fluid it contained. These figures, of course, represent extremes dangerous to life. Pigeons always die when 22 per cent. of the water in their bodies has been lost, and sicken when 11 per cent. has gone [Nothwang]; human beings similarly fall ill when water is too drastically withdrawn from them—the "crushed grain cure." Nothwang allowed pigeons to die of thirst, and observed that the muscles and a mixture of the other tissues and organs showed a greater loss of fluid than was recorded by Straub in his shorter experiments upon dogs. The dried residue was 6 to 7 per cent. greater. Less water is lost in simple starvation. Nothwang gives the following figures:

	In Muscle. Per Cent.	*Average of other Organs.* Per Cent.
In normal animals	23·04	26·96
In "thirst" animals	29·37	33·47
In fasting animals	18·36	25·43

In the thirsting pigeons the ratio of the dried residue to the mineral salts of the tissues was unaltered. In the fasting animals this was otherwise; 100 grammes of fat-free muscle normally contain 6·14 grammes of mineral matter, during thirst 6·18 grammes, and in starvation 4·96 grammes.

The extractives of the fat-free organs were increased by thirst [Nothwang (5)]; this indicates—at any rate, for these animals—that they were largely retained for lack of flushing out of the system.

(γ) *The Exchange of Protein.*

All researches made upon dogs, and most of those upon men, show a marked and progressive increase in the excretion of nitrogen during the period of thirst. This is illustrated by the table on p. 405.

It happens in a number of cases that the nitrogenous excretion wanes transiently for the first few days. Most authors put this down to retention of nitrogen; Spiegler attributes it to the dilatory absorption of the food which is in the intestine. But in these cases also the progressive rise in the nitrogen excretion invariably observed continues during the subsequent period, and is occasionally even more marked than usual. Under these circumstances, not only are the end-products of the previously decomposed protein washed away out of the body, but the decomposition of protein still goes on. The tissues continue to be deficient in moisture after the period of thirst for several days; injury has clearly been sustained by such portions of the protoplasm as possess less vitality. Possibly, too, the raised temperature noted during the later days of a period of thirst is connected with this protein decomposition. The nitrogenous loss that occurs when water is no longer withheld doubtless has the same significance as the epicritical loss of nitrogen observed in pneumonia, relapsing typhoid fever, etc. In each case it is probable that while the injurious influences persist, large amounts of protein are oxidized, but not completely. Their vital combinations are so far interfered with that on the return to normal conditions they can no longer be applied by the cell to its vital process, and so are broken up (5).

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[1] H. Salomon's observations upon stout anæmic girls agree with this in essentials. It is remarkable that the inspissation of the blood should have persisted in chlorotic persons after the thirst cure was over (7).

	Day.	*Nitrogen Intake.*	*Nitrogen in Urine.*	*Nitrogen in Fæces.*	*Nitrogen Balance.*	
Before	1	16·86	16·30	0·71	− 0·15	− 0·11
	2	16·86	16·15	0·71	− 0·00	
	3	16·86	16·00	0·71	+ 0·04	
Thirst period	1	15·71	15·71(?)	0·90	− 0·9(?)	− 29·6
	2	15·71	13·75	0·90	+ 1·06	
	3	15·71	17·55	0·90	− 2·74	
	4	15·69	18·39	0·90	− 3·60	
	5	8·7	18·74	0·90	− 10·9(!)	
	6	7·2	17·38	0·90	− 11·7	
After	1	16·26	21·24	1·56	− 6·5	− 30·4
	2	16·26	22·99	1·56	− 8·3	
	3	16·40	19·41	1·56	− 4·6	
	4	16·40	22·57	1·56	− 7·8	
	5	16·40	16·86	1·56	− 2·0	
	6	16·40	16·02	1·56	− 1·2	

To contrast experiments made upon animals under forced feeding with Dennig's, he often observed that after three or four days his animals no longer ate up the whole of their dry diet. Hence, considered as experiments upon the metabolism, his investigations were not ideally carried out. But from a practical point of view they are all the better for this, because the limitation of the input of water, which is ordered therapeutically, generally lessens the appetite [von Noorden]. When the food and nitrogen given were diminished, the excretion of nitrogen in the urine increased, attaining heights that were not reached if other conditions remained the same and water was given freely. The following table summarizes the nitrogen balance-sheets recorded by Dennig [5]:

	Thirst Period.		*After Period.*	
	Length of Experiment.	Nitrogen Balance.	Length of Experiment.	Nitrogen Balance.
	Days.	Grammes.	Days.	Grammes.
Thin person ..	6	− 29·6	6	− 30·0
Thin person ..	5	(− 4·7) Food intake diminished during thirst period	6	(− 0·7) No analysis of fæces
Fat person ..	7	− 25·8	5	− 3·7
Fat person ..	6	− 9·0	6	− 20·0
Fat person ..	6	+ 1·5 Not diminished	6	− 15·5

The varying extent of the nitrogen losses here is explained in part by the various quantities of water lost. The corpulent persons, who no doubt contained relatively more water at the outset, lost less fluid by their lessened perspiration than the thinner individuals. Similarly in animals, the sudden and thorough removal of water from the system [Straub] upsets the nitrogen balance-sheet more than does the gentler accomplishment of the same end [Spiegler (5)].

(δ) *The Urine and Fæces.*

The ratio of the urea to the total nitrogen was about normal in Dennig's researches (5). The behaviour of uric acid during a period of thirst is recorded only in an old investigation by Jürgensen (5). He used Heintz's method, and found 1·1 gramme of uric acid on days of thirsting; in view of the diet—rolls and ¼ pound of horse-flesh—the figure seems a little high. Sugar, albumin, and bile-pigments were not observed in the urine.

The urinary phosphates increased correspondingly with the excretion of nitrogen, or often even more rapidly during the first days [Landauer]. The fæcal phosphate was not estimated, so no further conclusions can be drawn. In a few investigations Landauer found that the excretion of the sulphates was not increased (5).

Dennig noted that the motions were abnormally dry in a few cases, both during and after the period of thirst. The utilization of protein and fat was practically unchanged, although this was not so during the subsequent period in certain cases in which diarrhœa was observed [Spiegler, Dennig, Straub (5)].

(ε) *Thirst and the Consumption of Energy—the "Combustion of Fat."*

According to Oertel, Lorenzen, and Schweninger (6), diminution of the water supplied to the obese augments the oxidation of their fat. This is said to occur when no change is made in the food consumed; in other words, the total oxidation increases. These authors support this view by theoretical arguments obtained inductively. But the view rests upon obscure physiological and mechanical suppositions, and is contradicted by our knowledge of the economy of heat in animals. And even theoretical reasoning would indicate an *a priori* lessening of the production of heat; for the skin becomes dry in thirst, and must give off less water, and so less heat too, etc.

Fortunately, we now possess certain experimental data which entirely overthrow these theoretical speculations. Landauer, in the most marked cases, found a mean increase of 8 per cent. in the excretion of CO_2 in his experiments. But his figures are unequal, and his dog did not keep quiet, so that his experiments are not conclusive. In Straub's (6) well-managed twenty-four-hour experiments the excretion of CO_2 was as follows:

	I.	*II.*	*III.*	*Average.*
Two days before ..	222·4	235·6	—	230 grammes CO_2
Three thirst days ..	228·3	231·2	222·6	227·4 grammes CO_2
Two days after ..	237·1	234·2	—	235·6 grammes CO_2

Here the loss of water was very great; the oxidative processes were quite unaltered. Researches upon man were slow in forthcoming, but have at last been made by H. Salomon (7). He examined the gaseous exchange during repose in five chlorotic and in two corpulent young women, both before, during, and immediately after a thirst cure. He made very numerous determinations—twenty-four, on an average, for each patient—and carried them out very carefully, so that they may be regarded as models for future work on the same lines. They proved clearly and decisively that in no case was the consumption of O_2 increased during a period of thirst.

Salomon diminished the fluid taken by his patients to about the greatest extent practicable. This makes his results speak the more forcibly against the theories of Oertel and Schweninger, which have now received their quietus.

Oertel lays stress upon the absolute limitation of the fluid drunk. Schweninger, contrariwise, withholds fluid during meal-times only. But to defer the consumption of water in this way has not the smallest influence upon the absorption of food in the intestine [Ruzicka (8)]. Nor has it any influence upon the metabolism—at any rate, upon that of adult animals—according to Spiegler's preliminary communication (9). Young and growing animals certainly do, however, fall behind the control animals, both in growth and in the amount of fat put on. Spiegler gives no analytical data, so that it remains uncertain upon what this depends.

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5. The Water Contents of the Tissues.

(a) *Variations in its Amount.*

Speaking generally, the amount of water in the body is pretty constant. If the diet of maintenance is given and remains unaltered, if the bodily activity (in experiments upon animals) stays the same, and if the climatic conditions do not change, the balance-sheet of the water and its quantitative relations often continue to be surprisingly uniform from one day to another [Bischoff and Voit (1)]. But in man these conditions are frequently not properly complied with, and then the body-water shows certain variations that do not impair the health in the smallest degree. In well-arranged experiments upon the metabolism, even when medical men are the subjects and when the urine and fæces are passed at regular intervals, one often finds variations of ½ kilogramme or more in the weight from day to day; such variations must, of course, be put down to the water.

Even at the present time the gain or loss of fat is often taken to be the same as the difference between the weights at the beginning and at the end of a series of experiments, due regard being paid to the nitrogen balance-sheet. Yet Voit long ago raised energetic protests against this practice. The increased transpiration occurring in dry atmospheres, in high temperatures, or in consequence of muscular exertion, leads to considerable losses of water, which are often made good only after forty-eight hours.

If the retention of 300 grammes of water in the space of five days were erroneously set down as a putting on of fat (= 2,850 calories), the daily oxidation of food would appear to be 600 calories lower than it really was. Voit has clearly proved that in dogs alterations in the diet can bring about considerable changes in the tissue moisture. These animals accumulate large quantities of water in their tissues when they are fed upon bread for a long time. One of his dogs lost no less than 900 grammes of water on the first day when transferred to a diet of meat. Bread, and bread only, is certainly an unphysiological diet for carnivores. It is not yet known whether the tissues of human beings on a purely vegetarian diet become richer in water than when a mixed diet is employed, and, if so, to what extent (1).

The decreased moisture of the body that occurs in the so-called "thirst cures" has been discussed above. Certain authors [C. Voit, Nothwang, Bidder, C. Schmidt, Sedlmair (2)] found the body more watery during simple inanition; many others did not. In most of these researches, of course, the determination of the water in the tissues freed from fat and dried—though indispensable—was not carried out (2). The fact that a single draught of water given during fasting is not always ollowed by a corresponding increase in the urine excreted rather indicates hat the tissue-water is lessened during starvation.

Little more is known about the variations in the tissue-water. The issues of the fœtus contain a great deal of water, the more the younger the œtus is [Fehling]. In old age the tissues are tough, and appear to be dry, but, according to J. Ranke, contain more water than they do in middle age. This author found 81·2 to 84·8 per cent. of water in the muscles of old persons in place of 75 to 80 per cent. (3).

Exact knowledge of the amount of water in the tissues is also of great importance to pathology. In cholera the dried residue of the tissues increases by 5 to 6 per cent. [Voit and others (4)]. This indicates, as was shown above, that 100 grammes of the tissues lose 20 grammes of water, a quantity of the same order of magnitude as the drying observed in thirst cures. In cholera the serum can become even more inspissated than it does when fluids are withheld, and densities up to 1,047 have been recorded [C. Schmidt (4)]. The behaviour of the body-water in the course of other diseases has rarely been systematically examined. Leyden (5) concluded from indirect evidence that the tissues become more watery in fever. But this idea was very justly attacked by Senator, and has received no confirmation from the few direct determinations that have since been made [Manassein, Salkowski (5)].

In order to appreciate properly the meaning of losses of water for the body, it is necessary to compare and contrast the quantities of that fluid and their distribution in the body. Apart from the freely flowing water that circulates in the blood, the lymph, and perhaps also in the cerebrospinal fluid, the water serves only to swell out or distend the tissues. It is so firmly united to the living or fresh tissues that not even the smallest part of it can be squeezed out by very great pressure.[1] Muscle substance does not part with any juice to pressure before autolysis has occurred in it [Vogel (6)].

(b) *The Relation between Protein and Water—the Influence of Various Stored-up Substances upon the Water Content.*

In general, about 20 to 22 parts of nitrogenous matter are soaked in, and swollen with, 78 to 80 parts—four times as much—of water. The fact that most organs contain more solid and less water depends upon this—that other solids, either without water, or containing only a little of it, are still stored up in them. The most important of these is fat. Fat enters into the interstices of the protoplasm as a dry and waterless mass, neither driving water out of the tissues nor bringing it into them. L. Pfeiffer (7) examined the organs of a number of fat and lean animals of the same species, and found that the amount of water contained in them was constant, if calculated for the tissue freed from fat. The fatty organs sometimes seem to contain 1 to 2 per cent. more water; this is perhaps an error arising from the difficulty or incompleteness of their drying [Nothwang (7)]. My own analyses have shown that in the adipose tissues the ratio between the quantity of protoplasm in the "membranes" and the water is practically constant in healthy animals. Here, too, the water of the tissues only serves to expand them; the fat stored up in the cells only fills them out into globular masses—without the fat they are flattened—and does not alter the quantity of water they contain. It is incorrect to state, as many authors have done, that when 100 grammes of fat undergo combustion and set free 107 grammes of oxidation-water, further quantities of "tissue-water" are also set at liberty. This would only be true if, in addition to the fat, the nitrogenous constituents of the adipose tissue also broke down. There is no reason to suppose that this happens when fat is lost; and, further, even if it were so, all nitrogenous losses are set out in calculations without reference to their origins as "muscle losses," and allowance is thus always made for the quantity of water they give rise to (7).

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[1] Note while going to press: This is confirmed by von Fürth and Schmidt-Nielsen (6).

To what extent the unequal accumulation of fat can affect the percentage of water in the body is easily understood, and has often been calculated. Lawes and Gilbert (8) found that a fat sheep contained 45·8 per cent. of fat, and only 35 per cent. of water; a lean sheep had 18·7 per cent. of fat and 57·3 per cent. of water.

The following calculation is inserted to illustrate the point in man. Bischoff's lusty labourer weighed 68·5 kilogrammes, and contained 40·3 kilogrammes of water and 28·35 kilogrammes of dried substance, 12·4 kilogrammes of which were fat. The percentages here are 59 per cent., 41 per cent., and 18 per cent., good mean figures for a man with an average amount of subcutaneous fat; Voit gives 63 per cent. of water, and 37 per cent. of dried substance. A man like this could easily contain either 5 kilogrammes more or 5 kilogrammes less fat, without changing his composition in any other way. In the latter case he would seem a little thin; in the other he would be well covered, but not unduly paunchy. The following table states the composition of his body under these various circumstances:

	Total Weight.	*Absolute Parts of—*			*Percentage of—*		
		H_2O.	Dried Substance.	Fat.	H_2O.	Dried Substance.	Fat.
		Kg.	Kg.	Kg.			
Bischoff's labourer ..	68·65	40·30	28·35	12·4	59·0	41·0	18·0
The same with 5 kilogrammes more fat..	73·65	40·30	33·35	17·4	54·7	45·3	24·0
The same with 5 kilogrammes less fat ..	63·65	40·30	23·35	7·4	63·4	36·6	11·6

The deposition of fat would, of course, affect calculations concerning the water contained in the separate organs in similar ways. Hence the fatless muscles of starving animals cannot be compared directly with the fat-containing muscles of the normally fed animal. Only the calculations made for the fat-free tissues can be compared with one another.

It may be stated, therefore, as a general rule, that when the fat is considerably lessened the ratio of protein to water is not perceptibly changed. But certain exceptions may be mentioned here. One cannot be certain that, when the cellular fat has almost entirely vanished and the fat cells collapse, small quantities of albuminous fluid do not pass into them and make the tissue more watery. It is more probable that some such process occurs in those tissues or organs that are enclosed within dense walls which do not permit of any diminution in their volume, even though their solid components have disappeared. The brain is but little affected by these considerations. Its weight is not much decreased during starvation, and even a considerable lessening of its volume can be made good by distension of the lymph spaces surrounding it. But with the bone-marrow things are otherwise. If the fat vanishes, and cannot be replaced by the multiplication and deposit of new cells, a vacuum is made that can only be filled up by the entry of fluid. Zuntz tells me that he actually found the bone-marrow abnormally watery in a calf that had become thin through abnormal feeding. Numerous observers have recorded an increase in the water contained in the bones in inanition [Chossat, C. Voit, Sedlmair, and others (8A)]. It depends upon replacement of the fat by albuminous fluid from the tissues. In the bones, the absolute as well as the relative amount of water increases ; this is not observed in the other tissues.

Similar to the rôle of the fat in the rest of the body is the part played by the medullary sheaths of the nerve-fibres, and by the deposit of mineral matter in the compact bones. The glycogen in the liver can rise to 19 per cent., and in the muscles to 3·6 per cent. [Schöndorff (9)], and so can influence the relative amount of water they contain. Owing to the lack of investigations, it is impossible to say whether the glycogen resembles fat in being deposited as a dry waterless mass, or is laid down swollen with water. If the latter were the case, the accumulation of glycogen would involve the simultaneous increase of the absolute amount of water in the tissue. It is possible that the retention of water by dogs fed upon bread, which Voit records, may be explained in this way. The fact that when human beings lose carbohydrate they also give up water from their bodies may here be repeated for sake of comparison. Changes in the residue left by the blood on drying are not, as was at one time supposed, comparable with those of the other tissues of the body. The blood is a suspension of cells containing little water in a fluid containing much. A relative increase in the plasma may be caused either by the absorption of fluid from the tissues, or by the inadequate formation of new cells (= anæmia). The blood in this way becomes more watery, and poorer in cells and hæmoglobin, without practically affecting the distribution of the water in the rest of the body ; the opposite conditions are also similar.

Quite recently W. Engel (10) has examined in detail the deposition of water in the tissues by new methods. He injected large quantities of 6 per cent. NaCl solution intravenously, and found that all the tissues, except the bones (owing to their composition and mechanical resistance to fluid), become more watery. The muscles, skin, and kidneys take up the greatest percentage of water—3·86 per cent., 3·23 per cent., and

3·83 per cent. respectively; the muscles, representing some 40 per cent. of the weight of the body, take up more than two-thirds of this water, but continue to act normally, in spite of the added moisture.

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F.—THE METABOLISM OF MINERAL SUBSTANCES.

From a purely chemical point of view the metabolism of the minerals is not interesting, for they undergo chemical change to only a minor extent; and they take but little share in the transformation of energy, for they are not sources of energy, and probably play no part in its development [Köppen (1)]. Their significance for the organism is only partially understood. Exact experiments have proved that they are indispensable to the organism, and the amount in which they are required during growth has been investigated repeatedly (see the section on the Metabolism of Sucklings). But only a few serviceable determinations have been made upon the adult. The normal body takes up the organic food-stuffs to supply it with energy, in response to a definite demand. The mineral matter in the food is on a different footing; like water, it is absorbed in excess, or, putting the matter more carefully, in amounts far surpassing the necessary physiological minimum. The amount of the daily decomposition under definite conditions of life and nutrition—calculated on the basis of the urinary salts—is stated by von Noorden in the following approximate figures:

	Gm.		Gm.
Cl	6–8	Na_2O	4–6
P_2O_5	2–3·5	Fe_2O_3	traces
SO_3	2–3·5	CaO	0·15–0·35
K_2O	2–3	MgO	0·2–0·3

The decomposition of the alkaline earths, iron, and phosphoric acid is actually higher. They are only partially excreted in the urine.

The physiological minimum intake of mineral matter has been little investigated. Its determination offers great difficulty, since the same differences exist as in the case of the demand for protein or water, and these depend upon individuality and upon the variations of the organic diet. It seems hardly possible to give a "physiological optimum." A marked decrease in the amount of the salt supply must occur before any impairment of the metabolism becomes apparent. It is doubtful whether a moderate alteration in the absolute quantity or the mutual relations of the "food-salts" plays that important part in pathology and therapeutics which the numerous disciples of "physico-therapeutics" attribute to it. At any rate, no scientific proofs of its importance exist, and, above all, there is an absence of accurate knowledge of the physiological conditions here involved.

Were all the available information collected and published, together with the criticisms[1] for which it specially calls, it would need a volume to itself. At present it is only possible to write the prolegomena to "mineral physiology." The reader must not look for any so-called "sketch of the means which must be employed in the future," nor expect any exhaustive presentation of "the theory of osmotic pressure" in its significance for physiology and pathology. Reference will only be made to such questions as are of importance either physiologically in themselves, or else from the general standpoint of therapeutics, and are to be considered in regard to the "quantitative" examination[2] of "mineral physiology."

1. Chlorine (Sodium Chloride).[3] Sodium. Potassium.

Changes in the NaCl contents of the tissues are of practical as well as theoretical interest—as, for instance, in the conditions of uræmia, epilepsy, and hyperchlorhydria. A knowledge of the entire chlorine content of the body would be useful, but even in this regard, which presents slight analytical difficulty, there are countless untrustworthy statements, especially in regard to the chlorides in the tissues, in the food, and in the excreta.

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[1] In almost every case the methods of investigation employed, as well as analytical technique, would be called into question.

[2] The qualitative importance of mineral substances in the diet was emphasized by Liebig, Benecke, Voit, and others. The theory of osmotic pressure, etc., is to be found in the works of Köppe, Hamburger, Lazarus Barlow, etc. (1).

[3] The chlorine analyses are most often expressed as NaCl, which is quite inconceivable from the point of view of calculation. For the consideration of many questions, when the chlorine is definitely combined with both K and Na, it may be taken that 100 grammes of Cl are more or less equal to 165 grammes of NaCl; 100 grammes NaCl = 60·7 grammes Cl + 39·3 grammes Na. In using the factors just given it must be remembered that the "NaCl values" are only the values of the chlorine calculated as common salt, and that they do not indicate the amount of sodium actually present. On the other hand, the "chloride total" (NaCl + KCl) only gives the figures for Na and K calculated from the chlorides. The amount of the chlorine content is imaginary, and has nothing to do with the Cl really present—for instance, blood contains more alkali than would saturate the chlorine in it.

Chlorine is found in the serum of the blood, and perhaps also in other tissues, not loosely united with the protein bodies, like many other mineral substances, but always in an inorganic form. It is entirely diffused [Loewy and Zuntz, Gürber]. The relative constancy of the chlorine of the tissues is, therefore, not to be attributed to a combination with the organic substances, as Voit and Forster and others assumed (2).

The total amount of Cl and of NaCl in the body of a full-grown man is not known.[1] In a mouse Bunge (3) found 0·14 per cent. Cl = 0·23 per cent. NaCl. Seven analyses of new-born human beings gave an average of 0·188 per cent. Cl = 0·310 per cent. NaCl for the whole body. The extreme values were 0·138 to 0·194 per cent. Cl = 0·23 to 0·32 per cent. NaCl. If these figures are transferred to the adult, a body weighing 70 kilogrammes would contain 97 to 133 grammes Cl = 160 to 220 grammes NaCl. The body of an adult is probably poorer in chlorine than that of a new-born babe. But it may be supposed to possess at least 100 grammes NaCl.[2] Healthy human blood contains, according to the faultless experiments of C. Schmidt, Wannach, and Biernacki, about 0·27 to 0·28 per cent. Cl = 0·45 to 0·47 per cent. NaCl.[3] [Limbeck gives 0·65 to 0·73 per cent. (?)]. Human muscles[4] contain 0·0701 per cent. Cl = 0·116 per cent. of NaCl [Katz (3)].

(*a*) *The "Excess of Common Salt" in the Body—The Question of the Withdrawal of Salt.*

There is a widespread belief that, in consequence of man's habit of consuming an extravagant amount of salt, a certain superfluity of it remains in his body. How large this excess of salt consumed may be is best seen from investigations in which its disappearance can be traced —that is to say, when chlorine is completely, or almost completely, excluded from the diet. This occurs in fasting pure and simple, or in abstinence from NaCl alone.

In studying such balance-sheets it is only occasionally possible to count upon the determination of the Cl in the fæces. Excepting in diarrhœa, only traces—at most decigrammes—of chlorine are to be found in the stools. One isolated example, such as that of Klein and Verson (4), who found in the daily fæces, on an average, with a diet poor in NaCl, 2·6 grammes of NaCl, and with ordinary food as much as 8·8 grammes

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[1] There are no determinations of the chlorine in the separate organs either for man or beast. I have only discovered one analysis, made by Nencki and Simanowsky (3), of the chlorine contained in all the organs, and that was in the case of a dog.

[2] Five litres of blood contain about 23 grammes, 35 kilogrammes of muscles about 40 grammes of NaCl. The fatty tissues and the compact tissues of the bones are poor in salt, so that, subtracting these, the remaining tissues must be richer in salt than the muscles. Nencki's (3) figures from experiments on dogs actually prove this.

[3] Voila's (3) average value for human blood-serum (0·55 per cent. NaCl) agrees very nearly with the older figures, as serum contains 20 to 30 per cent. more Cl than blood. Abderhalden's chlorine analyses in eight species of mammals gave for the blood 0·238 to 0·309 per cent. Cl = 0·39 to 0·50 per cent. NaCl (3).

[4] According to Katz, the flesh of most other mammals rather contains less chlorine. Bunge found somewhat higher figures for ordinary ox flesh, 0·099 per cent. Nencki gives very low figures for the amount of Cl in dog's flesh, about one-third below those of Katz (3).

NaCl (!), is surely due to errors in the analysis, and raises doubts as to the trustworthiness of the other data given in their work. But analyses of chlorine in the food cannot be dispensed with. A so-called "uniform diet," in which the provisions for the whole experiment are not laid in beforehand, and the value of the "sausage salt," the most precious asset of the whole lot, has not been determined, by no means guarantees a uniform supply of NaCl. To my mind this objection applies to the meritorious and troublesome experiments made by Stadelmann's (4) pupils. They seem to have accepted the food provided by "the cook." Nowhere throughout their works have I been able to discover any guarantee for uniformity in the daily supply of NaCl, which, to judge by the figures given for the chlorine in the urine, must have been very large during these investigations.[1]

The Withdrawal of Sodium Chloride in Starvation, or in Abstinence from Salt.

Cetti, when fasting, in ten days excreted altogether 13·13 grammes Cl; Breithaupt, in 6 days, 7·2 grammes [J. Munk (5)]. After deducting the chlorine of the drinking-water and the "chlorine corresponding to the decomposition of muscular tissue," 11·0 and 6·2 grammes Cl were given off as "superfluous." In Belli's experiment, with a diet poor in common salt, in the first ten days 11·8 grammes of chlorine left the body, and this occurred almost entirely during the first five days; in the following five days equilibrium was more or less maintained. Also, in a similar experiment by Wundt, the total amount lost in five days certainly was not more than 10 grammes of chlorine. No figures are given for the chlorine in the food. Luciani and Freund's statistics, taken from Succi, are of no value for our purpose, owing to the fact that he was constantly drinking mineral waters rich in common salt (5).

The amount of chlorine given off by the body in these investigations we may look upon as the "excess" previously amassed; its maximum was 11 grammes Cl = 17·5 NaCl. It should be noted that the persons on whom the investigations were carried out contented themselves, as a rule, with "moderate" quantities of common salt—about 10 grammes with an average daily diet. It has not been determined whether larger amounts are amassed in the body in cases where it is ordinarily consumed in larger quantities—20 to 25 grammes NaCl.[2]

The excess of 17 to 18 grammes of sodium chloride observed in the investigations mentioned amounts to 12 to 15 per cent. of the probable total amount, which is about 140 grammes in a body weighing 60 kilogrammes. It is, therefore, not nearly as large as is generally supposed. But the whole of the 18 grammes of NaCl given off by the body must not all be considered as the "excess stored up"; it must be remembered with what tenacity the body retains sodium chloride after such privations, even when the supply is but moderate. In the first two days after his prolonged fast Cetti stored up 6·2 grammes of chlorine; Breithaupt in the same period 14 grammes; Belli in three days 4·3 grammes. In Luciani's case, also, the eager retention of salt after heavy loss was very apparent. The days on which Succi drank Riolo water were similarly indicated. *The small amount of sodium chloride left at the conclusion of the above experiments is by no means a "physiological optimum," but, rather, a "physiological minimum."*

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[1] It seems to us almost impossible that persons suffering from skin diseases, eczema, and advanced infiltration of the skin, and other affections, should be able to store up 100 grammes of chloride of sodium in the diseased portions of the skin. When S. Grosz, giving examples of his investigations in metabolism, produces cases in which persons suffering from skin diseases excreted 113 grammes NaCl more than healthy persons observed during the same five weeks and with the same diet, a doubt as to the effectual regulation of the diet must arise.

[2] Verson (4), who daily consumed 25·0 grammes NaCl, when the supply was restricted to 1·4 grammes NaCl during an eight days' investigation, excreted in the urine 35·8 grammes and in the fæces 22·3 grammes of NaCl. This showed a loss of 47·0 grammes NaCl, much more, therefore, than in the series of figures given above. As the figures for the fæces are undoubtedly wrong, it is questionable whether those for the urine should be accepted as right, and any calculations be based upon them.

Naturally, only a part of the loss of sodium chloride in these investigations was borne by the blood. At the end of a twenty-six days' investigation made by Forster (7) on a dog deprived of salt, the blood contained 0·22 per cent. Cl, the blood-serum 0·27 per cent.—that is, 25 per cent. less than the normal, which, according to Jahrisch and Abderhalden, varies from 0·28 to 0·29 per cent. for blood and 0·40 to 0·41 per cent. for serum. In Klein and Verson's observations on human beings the amount of NaCl sank from 0·42 per cent. at the beginning of the experiment to 0·283 per cent. after deprivation of salt for eight days; when salt was freely given again for four days it rose to 0·42 per cent. (?). In von Schenk's investigations upon animals deprived of salt the chlorine in the blood fell in some cases temporarily (?), in others permanently, as much as 50 per cent. Picard found only slight variations (7). These statements must be confirmed by further observations upon men and animals. It can only here be mentioned that Biernacki (7), who, with true critical acumen, employed the best of methods, observed very slight variations in the amount of chlorine in human blood in numerous cases of disease.

NaCl is excreted [Javal (8)] in cases of underfeeding, where the supply is small—for instance, with an exclusive diet of milk given in insufficient quantities. The loss is less than when no salt at all is taken, and chlorine equilibrium, or even retention, soon takes place.

A second method of withdrawing sodium chloride from the body consists in the administration of large quantities of alkaline carbonates, or of compounds of the alkalis with vegetable acids. As soon as these

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It is not impossible that, in further experiments as to NaCl and its loss, higher figures than the above may be obtained, and seem to be surely established. Such are to be found, for instance, in the case of dogs; they are to be considered as "individual" variations—that is to say, differences for which no sufficient explanation is to be found in the conditions which obtain. It seems to me permissible to quote them, although on the whole we do not include investigations as to NaCl in carnivorous animals. F. A. Falk's (6) two dogs offer a striking instance, and their chlorine analyses are to be relied on. The younger, thinner dog, weighing 8·8 kilogrammes, excreted in twenty-three days of starvation 218 grammes of urea and 2·76 grammes of chlorine; the old and fat dog, weighing 21 kilogrammes, 406 grammes of urea and 1·05 grammes of chlorine. That is to say, while the absolute "loss of flesh" was double in the latter, the absolute quantity of chlorine was only one-third of that of the younger dog. (Influence of age or of richness in fat ?)

are given the body becomes poor, not only in acid substances and in HCl,[1] but also at the same time in sodium and potassium. Practically speaking, the body becomes impoverished in NaCl [Bunge, Stadelmann, Harnack (10)]. The determinations differ indeed from each other in regard to the various behaviour of the carbonates and the salts of the vegetable compounds, of the potassium and the sodium (see below). Bunge, after taking 18·2 grammes K_2O in the form of citrate, excreted 6·1 grammes NaCl = 3·7 grammes Cl. But this moderate loss of NaCl was almost made up for on the following day. In another experiment a loss of 3·4 grammes of chlorine after taking potassium phosphate was fully compensated for within three days. Harnack states that after giving a small dog daily doses of 2 grammes of dried Na_2CO_3 in thirty days, half the entire amount of chlorine was excreted from its tissues. But his investigation only gives chlorine analyses for fifteen days; the total excretion of NaCl was 15 times 0·84 (not 1·0) = 12·6 grammes NaCl in all. Yet, according to our calculation, the dog would have accumulated just about that amount in the previous ten days when given a diet rich in common salt—5·19 grammes a day. Therefore, at the end of the fifteen days' alkali treatment, the dog had arrived at the same chlorine content in the body that he had had after a short period of starvation at the very beginning of the experiment! Large apparent losses of chlorine must be discounted—at least, in the works of Hagentorn and Kozerski—as is shown by the protracted investigations of Stadelmann's pupils, who took alkali in large quantities for several weeks. In Burchard's case the amount of Cl excreted was not affected by the alkali taken. In Hagentorn's nine days' experiment the increase in the excretion amounted to 5·91 grammes Cl; in Kozerski's thirteen days' experiment the increase was 33·1 grammes Cl, as compared with the normal figures[2] (10).

But this increased excretion must not be looked upon as a real "loss of Cl from the body," as no proportional introduction of common salt into the body is anywhere specified as having taken place.

The body may lose Cl in a third manner, namely, when vomiting is frequently repeated, or when the stomach is regularly washed out; investigations might be made with the view of employing such gastric lavage therapeutically.[3] Many patients with hypersecretion, after a test breakfast, or on the stomach being washed out every evening, yield daily 500 grammes of gastric contents with 1·5 grammes of free HCl[4]—that is, of chlorine not combined with any base. In one patient with dilatation of the stomach I obtained more than 3 litres of liquid, containing 10 grammes of free HCl, from a single washing.[5]

Here is a procedure—at any rate, for certain cases—by means of which chlorine may be withdrawn from the body in the form of free acid, and the alkalinity of the tissues be increased. There do not exist any exact figures for human beings with all the necessary chlorine analyses of the food, urine, fæces, and other losses. But probably the presence of as little as 3 to 4 grammes of salt in the daily diet is a sufficient protection against loss of chlorine. The patients, so long as their chlorine supply does not fall below this, will simply excrete so much the less Cl in the urine as they lose by the mouth. Thus, their blood, as a rule, does not become poor in chlorine [Biernacki (11)]. But when the salt supply is limited to 0·6 gramme Cl = 1 gramme of sodium chloride, as in Belli's fast, it should surely be possible to withdraw a certain amount of chlorine from such patients. For even under normal circumstances the production of HCl by the stomach, though lessened, yet continues to be clearly demonstrable long after Cl ceases to appear in the urine, owing to impoverishment of the system in chlorine—at least, this is so in dogs [Forster[1] (11)]. Much more, then, is this to be expected when the secretion of gastric juice is continual. Besides, it would hardly be possible to increase the alkalinity of the body by such "withdrawal of HCl." If the alkali, which is set free from the sodium chloride by the formation of acid in the stomach, is prevented, by continual washings of the stomach, from rejoining the HCl in the intestinal lumen or wall, then it does not remain in the body, but is excreted in the urine as carbonate [Simanowsky (11)]. So, too, if the HCl of the stomach is neutralized by the introduction of alkaline carbonate, corresponding quantities of alkaline carbonate also appear in the urine.[2] Therefore, the organism will lose not only chlorine molecules, but most certainly sodium as well, whether alkali is supplied or HCl is withdrawn. But neither process, apparently, is able to raise the alkalinity of the body as a whole *to any great extent or for any length of time* (11).

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[1] The sulphuric acid and phosphoric acid are little influenced [Hagentorn (9)].

[2] The urine contained Cl as KCl as well as NaCl.

[3] In excessive secretion of the gastric juice I have obtained good results in this way, simultaneously giving large amounts of carbonate of sodium.

[4] The above figures do not here refer to the Cl of the chlorides, but only to that of the HCl secreted.

[5] The urine of the next day contained no appreciable quantity of Cl.

(*b*) *The Effect of Salt in the Decomposition of Protein and the Water Content of the Body.*

Voit (12) found the nitrogenous decomposition in dogs was slightly increased by giving large or medium-sized doses of common salt; Weiske

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[1] With chlorine-free food the vomit contained 0·27 gramme Cl for 24 hours, but this only represents a part of the stomach contents.

[2] Harnack is right in the severe strictures he makes on the opinion, occasionally expressed, that "the alkaline carbonate introduced into the body by the mouth cannot act as alkali, since it is neutralized in the stomach." The case is exactly the same as that given above. The sodium set free by the decomposition of sodium chloride acts as alkaline carbonate if no HCl is there to neutralize it. Putting aside temporary and local disturbances of the metabolism of acids and alkalis, the exhibition of alkali invariably has the same effect on the economy of the system, whether it is brought into the stomach or is injected experimentally into the duodenum or into the veins.

A similar error underlies the belief that, throughout the whole period of decomposition, the body becomes richer in alkali in proportion to "the total amount of the gastric HCl." Let us suppose, as a help towards grasping the subject, though it does not altogether apply, that the whole amount of sodium set free as carbonate by the decomposition of $NaCl + H_2O$ into $HCl + NaOH$ enters into the lumen of the intestine together with bile, pancreatic juice, and intestinal juice, and here saturates itself again with the acids of the chyme. The secretion of these alkaline digestive juices begins at once, perhaps within half to one hour, after food has been taken. Hence, not taking into consideration the first period of digestion, nearly equivalent amounts of acid enter the stomach, and of alkali the intestines. Therefore the "juices of the body" do not become substantially richer in alkali, owing to the "formation of acids." It is not known whether the hyper-

and Feder observed the same results. More recent investigations contradict this [Gabriel, Pugliese, and especially the careful work done in Voit's laboratory by Dubelir, Straub and Gruber (12)]. According to Straub, the sodium chloride effects a reduction in the nitrogenous decomposition. It is only after large doses—0·6 gramme to 1·1 grammes per kilogramme — that increased diuresis occurs, and in the author's opinion the augmented nitrogenous metabolism is due to this.[1]

The effects of the withdrawal of only NaCl from the food have been well investigated in human beings. In Belli's ten days' experiment, with the chlorine of his food cut down from 6 grammes to 0·6 gramme, about 10·6 grammes nitrogen were excreted in all; the loss was greatest on the first days. On again taking the customary 6 grammes Cl, the nitrogen balance-sheet immediately showed a result positive but small. So here, too, the salt proved itself to be an "economizer of protein or nitrogen." On the whole, however, the influence of sodium chloride on the decomposition of protein in health is so slight that when the use of mineral waters containing common salt has a favourable effect, it ought not to be attributed entirely and without further inquiry to the small quantities of salt therein contained.

When sodium chloride is withdrawn from man, his weight decreases [Klein and Verson, Belli (13)], and more so than the "loss of flesh" accounts for; water is lost, together with the NaCl. The weight rises quickly as soon as common salt is supplied again. In starvation small doles of NaCl increase the water contained in the tissues [Pugliese], and render the animals more capable of resistance. Succi, when fasting—perhaps for this very reason — instinctively took small amounts of mineral waters during his thirty to forty days of starvation. When deprived of common salt the blood becomes somewhat concentrated; it contains only 78·2 per cent. H_2O against 79·1 before the experiment and 79·9 after [Klein and Verson]. Other organs also lose water. The parallelism between the balance-sheets of NaCl and water is partly to be explained by the theory of osmotic pressure, as is also the diuretic effect of large doses of sodium chloride. Under their influence the water abducted by the large quantities of NaCl, which have to be excreted in the urine, far exceeds the water adhered to by the small quantities of salt, which remain in the body for the most part (13).

Common Salt and Absorption of Fat.—If 10 grammes of NaCl be given, they have no effect on the fat absorption in human beings; 20 grammes may be injurious, in so far as they overstimulate the intestine [Coggi (14)]. This is, however, not always the case with persons who habitually consume much salt with their food.

The replacement of chlorine by bromine, and the relation of common salt to the osmotic pressure, is dealt with elsewhere.

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secretion of an abnormally acid stomach-juice corresponds to the similar increase of the other digestive juices and to a larger amount of the alkali therein contained. The question might well be studied in dogs with "Pawlow's gastric and pancreatic fistulæ."

[1] Here, too, the results of experiments on carnivorous dogs or on wethers must not be applied to human beings. Dogs have been fed with as much as 1·1 grammes NaCl per kilogramme; 0·3 to 0·5 are here given as medium values, whereas such figures are seldom attained, even experimentally, in human beings.

(c) *Alkaline Carbonates and Compounds of the Alkalis with Vegetable Acids.*

The alkaline compounds of the vegetable acids undergo combustion in the body, and therefore ultimately exert the same effect as the alkaline carbonates. Their influence on the economy of the nitrogen, the common salt, and the alkalis is, according to Stadelmann, exactly the same as that of the carbonates. Harnack (15) denies this so far as the removal of Cl is concerned; carbonate of sodium effected an excretion of chlorine in his dog; equivalent quantities of sodium or potassium citrates, etc., did not produce such an effect. But in these investigations on the carbonates the dog had been given 4 grammes NaCl, in addition to the chlorine contained in his food, and thus had retained Cl in his body before the beginning of the experiment. This had not been the case in the investigations on the alkaline salts of the organic acids. This question has, therefore, still to be finally settled. The supply of carbonates is certainly much more important for the intestinal tract than the supply of the salts of the vegetable acids. After sodium carbonate has been taken, partial or complete saturation of the HCl of the stomach and increased alkalinity of the intestinal contents ensue; after organic acids have been taken they replace the free HCl of the stomach. Whether the salts of the vegetable acids produce an amount of alkalinity inside the body equal to that produced by the equivalent quantities of sodium carbonate, depends upon the locality in which the change into carbonate takes place.[1] Further, it must be considered whether the Na_2CO_3 *in statu nascendi* acts as powerfully as, or more powerfully than, that which enters the cells having been already formed outside them. Yet another difference might arise if the alkaline carbonate formed in the body was excreted either more or less quickly than that introduced in a ready-made state, etc.

2. Phosphoric Acid. Lime. Magnesia.

(a) *The Decomposition of Phosphoric Acid.*

Ehrström, from a series of balance-sheets in experiments dealing with phosphorus, considers the minimum of phosphorus needed by a human being to be 1 to 2 grammes of P = about 3·4 grammes P_2O_5 a day, = 0·06 gramme P_2O_5 per kilogramme per day. It hardly appears likely that the consumption would fall below these values.[2] More recent experiments on dogs show also that the smallest amount of P_2O_5 needed is as much as 0·03 gramme [L. F. Meyer (16)] per kilogramme per day.

When the supply of phosphoric acid is inadequate, the body is by no means able to limit its output to the same degree as is possible in the case of chlorine under similar conditions. Both in complete starvation [C. Schmidt, F. A. Falk, J. Munk, Luciani, O. and E. Freund] and when the food contains as little salt as possible [Forster] the organism up to the very last gives off very considerable quantities of phosphoric acid; even more in positive starvation than in "deprivation of salts" (17). The reason for this is that in the former case the decomposing protein of the organs sets free "the salts bound up with it," and allows them to pass into the excretions. In the latter case, on the other hand, the protein of the food, which is poor in minerals, is largely consumed, whilst only small quantities of the protein of the body, which is rich in salts, are used up.

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[1] Irrespective of any specific effects of the organic acids and ofj their intermediary products of combustion.

[2] Maurel gives 0·04 to 0·05 gramme P_2O_5 per kilogramme.

Some part of the "salts set free" from the protein of the organs may be retained, during deprivation of salts, for the needs of the organism, and used once more when the protein of the body is again built up out of the protein of the food, which in this case is poor in minerals. But this does not occur to nearly the same extent with phosphoric acid as with chlorine; also, in human beings, the loss of phosphoric acid is much less when the diet is poor in salt only than it is in complete starvation [C. Tigerstedt, Renvall; see also Sivèn's experiment (18)].

Tigerstedt observes that with increasing amounts of phosphoric acid in the food, its balance-sheet shows better results. This often occurs if the P_2O_5 of the diet has previously been insufficient. The relations are thus the same as for the protein economy.

(b) *Topography of the Metabolism of Phosphoric Acid—The Relations between Organic and Inorganic Phosphoric Acid.*

Many attempts have been made to determine where, and in what form, phosphoric acid is retained in the body, and where, and from what sources, the body draws upon it for excretion. On the one hand, the balance-sheets of phosphorus may be used for a topography of the metabolism (von Noorden's "Local Diagnosis of the Processes of Metabolism"); on the other hand, they may be used to determine whether the inorganic phosphoric acid in the body passes on into organic combinations—that is to say, whether it can be employed in the building up of lecithin, nucleo-albumins, and proteins.

What amount of the phosphoric acid retained reaches the bones, what portion is devoted to the soft tissues, and how much of it remains organically combined in the body? To answer these questions accurately is a difficult matter. Here, again, an attempt is made to establish the fact that one element remains, by tracing the fate of some other element which is bound up with it in the metabolism.

1. *The Division of Phosphoric Acid between the Bones and Soft Parts.*

(*a*) The "flesh" of the body contains nitrogen and phosphoric acid in a certain proportion. This is fairly constant in the same organs of the same species, but varies greatly in different organs and different kinds of animals. If "flesh" is put on, phosphoric acid is retained; if protein is lost, the loss of phosphoric acid is simultaneous, and, according to E. Bischoff (19), in almost the same proportion as that in which the two are present in the "flesh" of the muscles. A certain parallelism is actually often to be seen between the progress of the nitrogen and phosphorus balance-sheets [see, amongst others, the investigations by Sherman, Renvall, Lüthje, and others (18)]. For instance, it occurs where a real building up of the tissues is going forward—that is to say, where the organism is growing, during convalescence, etc. But under other circumstances, and with adults, this parallelism is by no means always met with.

For example, Ehrström found the following balance-sheets in three series, of which the second and third belong together :

	Nitrogen.	*Phosphorus.*		*P_2O_5.*
1. Seven days	−9·3	+4·3	=	+9·8
2. Six days	+3·5	+3·8	=	+8·7
3. Six days	−10·9	+1·3	=	+3·0

that is, a heavy loss of nitrogen goes with a marked increase of P_2O_5.

For an exhaustive criticism of such investigations it must be remembered that it is by no means possible to apply the proportion of phosphorus contained in the organs of one class of animals to those of another. It is not permissible, as F. A. Falk has contended in opposition to Bischoff, to calculate the dwindling phosphoric acid in the flesh of a dog on the basis of figures obtained from the stall-fed ox. Secondly, it is to be observed that in these calculations, as a rule, it is the phosphoric acid contained in the muscles which is measured, whereas the "flesh" which is put on or lost contains within itself the substance of the muscles and of other organs in unknown relative proportions. Very little is known of the phosphoric acid contained in the different organs.[1] Further, it is uncertain whether, when the organs dwindle in mass, they give off nitrogen and phosphoric acid in the proportion in which they originally contained them. It is probable that organs rich in nuclei become relatively richer in P_2O_5 during starvation, as the loss of substance affects the body of the cell more than the nucleus which is rich in phosphoric acid.

In spite of all these uncertainties, the usual calculation that phosphoric acid in the "flesh" is put on, or given off, according to the $\frac{N}{P_2O_5}$ quotient cannot at present be set aside. In human muscular tissue the relation between nitrogen and phosphoric acid is about as follows :

$$\frac{N}{P_2O_5} = \frac{100}{13{\cdot}7} = 7{\cdot}3\,;\quad \frac{N}{P} = \frac{100}{6} = 16{\cdot}7.$$

According to this, should both N and P_2O_5 be retained simultaneously in an experiment, the nitrogen gained will immediately be laid up as creased "flesh," and the phosphoric acid present in this flesh is calculated by the above-given formula.

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[1] Thus the P_2O_5 content of the blood [Abderhalden (20)] is always far lower than that of the flesh [Katz]; it often contains only one-third the quantity. The liver and spleen in adults and oxen, on an average, contain 1·26 to 1·37 P in 100 grammes of the dry organs [Fr. Krüger]; the muscles of the same, according to Katz, contain only 0·71 to 0·74 per cent. P (20). For the P-content of the other organs sufficient determinations do not exist (20).

(β) In this calculation, should any phosphoric acid be left over, it is ttributed to the metabolism of the bones. That the skeleton grows maller during starvation[1] has been proved by numerous starvation xperiments on animals. Naturally, as soon as food is freely taken, it ecomes heavier again. By a continuous examination of phosphorus balance-sheets in investigations of the metabolism, Forster (21) was he first to demonstrate the fact that the bones gave off phosphoric acid. His dog, when deprived of salts, lost 32·8 grammes of phosphoric acid, of which, according to the author's calculation, two-thirds came from the bones and one-third from the other organs. Similarly, he found that the large amount of chalk—more than 13 grammes of Ca—lost by his dog arose, for the most part, from the bones. From a similar comparison of phosphorus and calcium balance-sheets,[2] J. Munk (21) has shown that "a melting down of the bone substance" occurs in both starving men and dogs. Luciani's and O. and E. Freund's investigations of Succi's fast prove the same thing. Forster (21) has also pointed out that these absolutely high losses of phosphorus from the bones can only be demonstrated by investigation of the metabolism. This is because they are so slight when compared to the enormous store contained by the bones that they are difficult to prove even by analyses of the bones themselves.

With insufficient food, as in starvation, the loss of P_2O_5 is often relatively greater than is the giving off of nitrogen, so that here, too, the bones seem to take their share in the loss. In thirteen days Sivèn (November 9 to 21) parted with 20·0 grammes nitrogen and 7·6 grammes P_2O_5; Renvall, in thirty-two days, with 91·8 grammes nitrogen and 21·5 grammes P_2O_5. Only 2·7 grammes and 12·5 grammes P_2O_5 were lost from the "flesh" as compared to the nitrogen excreted, so that 4·9 grammes and 9·0 grammes P_2O_5 came from other sources—that is to say, from the bones (21). Many authors believe that under these circumstances, the compact bone substance only gives off portions of its mineral substances—that is, undergoes "demineralization." But it is more probable that the fundamental organic substances—the gelatinous tissues—are diminished, perhaps on the inner and outer surfaces of the bones, or in their spongy tissue.

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[1] Concerning the metabolism of the bones in starvation, the percentage of the loss of weight varies in the bones of starving animals as compared to the bones of normal animals. The absolute values must be received with reserve, because the animals which were starved seldom had the same original weight of body or of bones as those with which they were compared. But in almost all the trustworthy experiments the bones lost very considerably in weight [Chossat, C. Voit, Lukjanow, and Sedlmair], but comparatively much less than did the other organs (20, A). Only Weiske and Sedlmair have instituted a complete analysis of the bones (dried substance, fat, H_2O, ossein, and mineral matter). From their figures it is apparent that the fat of the bones disappears almost completely during starvation. Its decrease accounts almost entirely for the loss of dry substance. At the same time little ossein and mineral matter are lost [Sedlmair]. The fat of the medullary spaces is replaced by water, or rather by a tissue containing much water, and the percentage of water in the bones rises, even if the H_2O content is reckoned on the substances freed from fat. The bones of starving animals contain not only relatively, but also absolutely, more water than those of normal animals [Weiske, Sedlmair].

A vacuum is formed in the unyielding bone—which cannot alter its volume—by the disappearance of the fat, and is filled up with fluid. The relations between the ossein and the mineral matter, and also those between the separate constituents of the ash, remain practically unaltered in starvation [Weiske, Sedlmair].

The constancy of the relations between the separate components of the bones, and the strength of their mutual union, is plainly seen from a most interesting observation made by Hans Aron (20, A). The small quantities of sodium and potassium always present in the mineral components of the bones cannot be entirely got rid of by boiling the minerals in water. The amount of potassium remains unchanged in severe disease of the bones.

[2] J. Munk, who believed himself to be the first to prove the shrinkage of the bones by means of simultaneous CaO and P_2O_5 balance-sheets, overlooked the fact that Forster had already pursued this method with success. Forster published his observations in two papers.

Up to the present time, the formula for the putting on of x grammes nitrogen and y grammes phosphoric acid has been as follows :

With x grammes of nitrogen, $\frac{x}{7 \cdot 3}$ grammes of P_2O_5 are put on as "flesh" (p. 423), so that $y - \frac{x}{7 \cdot 3}$ grammes are left for the metabolism of the bones.

2. *Partition of the Phosphoric Acid between the Bones, "Flesh," and Organic Phosphoric Acid.*

Following the example of Forster and of J. Munk, attempts have recently been made to ascertain more exactly the metabolism of phosphorus by evaluating the balance-sheet of the lime for the same period [Mohr, M. Kaufmann, M. Dapper, Büchmann, Lüthje (18)]. The calcium of the bones maintains an almost constant relation to their phosphoric acid. The mineral substance of the bones contains a large amount of tricalcium phosphate, but little calcium carbonate, etc. For human bones, Lüthje, basing his calculations on Zalesky's figures, gives 0·73 gramme of phosphoric acid for 1·0 gramme of lime. Only a trace of lime is contained in muscular tissue—according to Katz, only 0·010 gramme CaO in 100 grammes of fresh human muscle. That of the other organs, excepting the spleen, is also so low that the total of lime for the soft human tissues does not amount to 10 grammes.[1] In the bones, nearly 100 times as much is stored up. It therefore seems to be altogether justifiable to attribute any large increase or decrease of lime entirely to the metabolism of the bones.

The following figures are calculated from the balance-sheets for lime, nitrogen, and phosphorus, taken simultaneously :

1. For x grammes of lime retained, $x\,0{\cdot}73$ gramme P_2O_5 are retained by the bones.
2. For y grammes of lime retained, $y\,0{\cdot}137$ gramme P_2O_5 are retained by the flesh.
3. Any residual P_2O_5 $[= z - (x\,0{\cdot}73 + y\,0{\cdot}137)$ gramme$]$ must be regarded as due to the putting on of organic phosphoric acid.

If, after the amount taken up by the bones has been subtracted, the quantity of phosphoric acid left is not enough to correspond to the nitrogen put on by the tissues, the gain of nitrogen is not termed "a gain by the tissues or flesh," but a gain from the protein reserve ["the incorporation of dead cells," Dapper, Lüthje, and others].

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[1] There are too few lime analyses available to make more detailed statements. The above figures are too high rather than too low.

3. *Criticism of these Calculations.*

The Retention of Lime.—The correctness of this view depends on the premise that any considerable quantities of lime can alone be stored in the bones alone, and that only when in combination with phosphoric acid. This opinion has many adherents, but an investigation made by Herxheimer contradicts it. Within eight days he retained no less than 16 grammes of lime without any corresponding gain of phosphoric acid.[1] He had consumed large quantities of calcium carbonate. But even with normal food conditions the lime and phosphorus balance-sheets often run diversely [Gottstein and Renvall (22)]. The latter, in a thirty-two days' experiment, retained 2·8 grammes CaO, and lost, in addition to 92 grammes nitrogen, 21·5 grammes P_2O_5. Rey (23) has further shown that lime, injected subcutaneously or intravenously into a dog, after an interval of three or five days still lingers in the body to the extent of 50 per cent., whilst the liver, spleen, kidneys, and walls of the intestine contain but the "merest traces." The amount of lime in the blood for three to four days after the injection was twice as great as the normal amount. Therefore, lime—probably in the form of carbonate—can for a time be stored up in the body in large quantities. Certainly for the most part it remains in the bones[2] without causing any substantial alteration in the percentage of the composition of the bones by its higher content of tricalcium phosphate.

These examples show that—under certain conditions, at any rate—the metabolism of the lime is independent of that of the phosphoric acid. This knocks the bottom out of the foregoing conclusion, that certain persons have drawn from the parallelism exhibited by CaO and nitrogen. We admit that the calculation runs fairly smoothly in many investigations—for instance, in Lüthje's experiments I. and II.[3] The total amount of phosphoric acid here divides itself evenly into "gain for the bones and flesh," in accordance with the figures for the lime and nitrogen, without leaving any excess or deficit. But the subjects on each occasion were convalescents, in whom not only a regeneration of the tissues, but a building up of the bones, was to be expected. The same arguments apply to the organisms of sucklings and animals that are growing. But it is more than questionable whether, in the case of an adult put on an extra diet, so quick and abrupt a change in the mineral metabolism of the bones occurs as the figures of some authors would lead one to suppose. For this reason any further conclusions as to the gain or loss of organic phosphoric acid drawn from such calculations are of little weight; and this is more or less generally admitted to be the case.

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[1] Compare, too, Rumpf (22).

[2] I may here refer to Weiske's figures (23A). In a small rabbit, fed on oats, which are poor in lime, supplemented by $CaCO_3$, there was a far larger percentage of lime and carbonic acid in the fatless dry substance of the bones than in another rabbit kept in the same way but without $CaCO_3$. The former contained 7·6 per cent. and 8·4 per cent. $CaCO_3$, calculated from the CO_2, in the mineral matter of the bones, against 5·5 per cent. and 6·2 per cent. in the latter. The bones of the former were richer in CaO in relation to the P_2O_5 than those of the latter. The ratio $\frac{CaO}{P_2O_5}$ was 1·34 and 1·35 in No. 1; in No. 2 it was only 1·27 and 1·29.

[3] Also in the clearer and more illuminating experiments on fasting animals conducted by Forster and Munk.

(c) *Metabolism of the Organic Phosphoric Acid.*

The question of the significance of the organic phosphoric acid has also been attacked from another side. It has been asked whether a supply of organic phosphoric acid is a necessity; whether the body cannot supply its own demand for nucleo-proteides, lecithin, etc., out of protein or fat and inorganic phosphoric acid.[1] However unlikely this view may appear, it cannot be directly contradicted, especially when one considers that the retention of phosphoric acid is generally larger on a diet of nucleo-albumin[2] than it is when the food contains phosphorus together with proteins free from phosphorus [Röhmann (24)].

A large gain of P_2O_5 is frequently, but not invariably, obtained when nucleo-proteides and nucleic acid [Loewi] or lecithin [Büchmann (25), and others] are added to the other food; but whether it actually is put on in an organic form is not to be determined by means of this method alone. The significance of organic phosphorus is evident from the large amount of this substance contained in the milk during lactation. Stoklasa (26) affirms that human milk contains no phosphate whatever. If that were true, the possibility of doing without inorganic phosphoric acid would be established—at any rate, in principle. Weiske and Steinitz (26) were able to keep animals for many weeks on casein and other food containing little or no phosphates. The health of these animals remained good, although the phosphorus equilibrium was not maintained. Thus the tissues can sometimes exist without inorganic, but hardly without organic, phosphoric acid.

It is not easy to definitely demonstrate the retention of organic phosphorus. In the same way, the loss of organic phosphorus can rarely be recognised, owing to the fact that it occurs in the urine in combination with a number of other products. In a case of acute leuchæmia, the patient was fed on a purely milk diet, and excreted 15 grammes of P_2O_5 during the last forty hours of his life, also excreting almost 12 grammes of uric acid (27). Here both products were certainly derived from the nucleo-proteides. But this would be far less easy to prove during the course of chronic leuchæmia.

(d) *Magnesia.*

Renvall, from his own and other investigations, calculates the demand for magnesia to be 0·75 gramme of MgO daily. In his experiments, the

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[1] There is no doubt that the suckling provides its own nucleo-proteides from the nucleo-albumin it receives.

[2] This was the case in the experiments of Steinitz and Zadik, though not in those of Leipziger (24).

MgO balance-sheet followed that of the CaO, and both gave positive results at a time when nitrogen and P_2O_5 were being lost. In Gottstein's investigations upon dogs the MgO balance-sheet ran parallel to those of the nitrogen and of the P_2O_5, in contradistinction to that of the lime (28). The disagreement between the relations here observed cannot be explained.

Iron and sulphur are considered in an earlier section, and iodine is discussed in the chapter on the Thyroid Gland.

3. The Expulsion and Replacement of Inorganic Elements in the Metabolism by Means of others closely allied to them.

(*a*) The Halogens.

The chlorine of the body can be largely replaced by bromine, but by iodine only to a small extent. After large amounts of the salts of bromine or iodine have been given, the gastric secretion of the dog contains considerable quantities of free hydrobromic acid, but little of the corresponding iodine combination [Külz, Nencki and Simanowsky (29)]. Iodine, which is far from resembling chlorine, remains in the body in small amounts only, and it is rapidly excreted. Bromine is more like chlorine, and is excreted very slowly, and when dislodged by the chlorine accumulates in the organism to a large extent. Nencki and Simanowsky found more bromine than chlorine[1] in almost all the organs of two dogs treated with potassium bromide. At the same time they noted that the absolute amount of bromine kept almost parallel to that of the chlorine in the various organs, whether they were rich or poor in the halogens. As a matter of fact, the chlorine was replaced by bromine. This is proved by the fact that there was a marked decrease of chlorine in most of the organs. But the sum total of the molecules of Cl and Br was greater than the number of chlorine molecules in the case of five healthy control animals. Besides the displacement of chlorine by bromine, a large number of other bromine compounds were formed.

The conditions are similar when dealing with the human subject, although not quite so clearly defined, as smaller doses of bromine have to be employed. The results of the bromine experiments of Tondo and Laudenheimer show that the excretion of the salts does not occur for several days after their administration. With a daily dose of 6 grammes of KBr, only 0·1 gramme is excreted in the urine during the first few days. Some days elapse before the amount excreted approximates to the amount administered.

The mutual displacement of chlorine and bromine can also be demonstrated in man, a dietary poor in NaCl appearing to favour the retention of bromides, whereas the addition of NaCl to the diet is followed by an increased excretion of bromides [Tondo]. The reverse holds good, bromides accelerating the excretion of chlorides. Laudenheimer found that, after the administration of 70 grammes of NaBr in seven days,

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[1] Some organs contained almost as many bromine as chlorine molecules. Compare the analyses of Buchner and Fell (29).

36 grammes were retained, while 26 grammes of sodium chloride were liberated and excreted (30).

(*b*) Alkalis and Alkaline Earths.

Comparable to the partial displacement of chlorine by bromine just described, it is easy to conceive of a displacement of sodium by potassium, especially as the latter is a normal constituent of the body. Bunge is at present engaged in observations on this point (31). He noticed that after the administration of large doses of potassium the sodium excreted in the urine increased by several grammes. But his observations were only made during one day. Forster's suggestion that possibly only the excess of sodium chloride present in the body was displaced by potassium chloride appears to be correct. Dogs fed on normal diet and on diet containing but little sodium showed no diminution of sodium salts or demonstrable increase of potassium salts after the administration of a fair amount of potassium [Kemmerich, Forster (31)]. This proof could only be considered complete if the dogs had been given large quantities of potassium. Considering the different biological value of the two alkalis, and their unequal distribution in the various tissues of the body, an extensive displacement of the one by the other does not appear very probable.

The appearance of minute quantities of abnormal elements in the juices and tissues, or of unusual constituents in the body after large doses have been administered, should not be ascribed to chemical displacement or substitution without further evidence. Weiske (32) noted that, after giving strontium carbonate instead of calcium carbonate, traces of strontium were present in the bone-marrow or periosteum, but not, as previous observers had found (1), in compact bone. An increased intake of magnesia is not followed by their definite deposition in bone [Weiske].

The experiments on growing animals supply striking evidence against any "physiological interchange" of calcium and strontium oxides. The animals were given food containing excess of potassium, but only traces of calcium oxide. In addition to their food, either strontium or calcium carbonate was administered. The bones of those animals to whom calcium salts were given developed normally, but the dogs that were taking strontium were attacked with severe symptoms resembling those of rhachitis [Cremer, Weiske (32A)].

4. Osmotic Pressure.

The osmotic pressure of the tissue fluids—most simply measured by the lowering of the freezing-point—depends on the amount of dissolved molecules and ions contained. Under physiological conditions its magnitude varies very little in the same species. For the human serum it amounts to −0·56°, the concentration corresponding to that of a 0·9 per cent. NaCl solution.

Of the total number of dissolved ions and molecules, according to Hamburger (33), 25 per cent. consist of non-electrolytes—that is to say, of organic substances — 75 per cent. consist of electrolytes, or inorganic salts. Two-thirds of the latter are composed of NaCl, and one-third of other salts.

Distribution of the Osmotic Pressure in the Serum.

From (1) non-electrolytes	.. ..	25 per cent.
(2) Electrolytes ..	.. ..	75 ,,
(a) Chlorides	.. ..	50[1] ,,
(b) Other salts	.. ..	25 ,,

Among organic molecules the osmotic pressure of albumin need not practically be considered; that of urea, grape-sugar, and creatin[2] is more important, and is somewhat raised by the actual increase of these salts in disease. Sodium carbonate is the most important of the salts other than chlorides, the osmotic pressure of the remaining salts present being very low. When blood shaken up with CO_2, and sodium obtained from serum albumin or from blood cells thus becomes diffusible, the osmotic pressure is slightly raised.

A similar collection of CO_2 and liberation of sodium takes place in blood circulating through the capillaries. A certain compensatory change takes place through the passage of chlorine (in combination with potassium ?) from the serum to the corpuscles.

The uniformity of osmotic pressure under healthy conditions is in part due to the constant proportion of sodium chloride present, which exerts 50 per cent. of the osmotic pressure. Even in illness the proportion of sodium chloride and the osmotic pressure vary but little, the only important alterations being seen in uræmia and similar conditions.

Mutual Replacement of the Molecules and Ions with Respect to the Osmotic Pressure.

With respect to osmotic pressure, ions which replace others to which they are closely related can also mutually replace each other in the body. But that a diminution of the electrolytes can be compensated for by an increase of organic substances is not to be assumed without further proof. If the osmotic pressure diminishes owing to a decrease in the amount of NaCl present, a compensating rise by means of an increase in the amount of sodium carbonate can hardly occur to a sufficient extent. The increase of phosphates in blood-serum on removal of sodium chloride, which has been observed by v. Limbeck and others (34), is too slight to be compared to the loss of chlorides as far as osmotic pressure is concerned.

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[1] Serum contains more NaCl than blood; in human serum there is 0·55 per cent. NaCl.

[2] Also an increased quantity of organic acids in the blood (lactic acid, oxybutyric acid, etc.) tends to raise the osmotic pressure.

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G.—METABOLISM IN OLD AGE.

As far as our present knowledge goes, metabolism in old age does not present any qualitative difference from that of adult life. Such differences do occur in infancy, when the body cannot yet accommodate itself to the inception of a varied diet. Old age, which is characterized by a slow atrophy of the body, does not exhibit any new or peculiar phenomena, but only a gradual weakening of metabolic powers.

1. The Energy Exchange.

The cells of the body lose their thermo-dynamic powers with old age. An old man utilizes less food, not only because his output of work is less, but also because his cells generate less heat during rest [Andral and Gavarret, Quinquaud, Tigerstedt and Sondèn, Magnus-Levy and E. Falk (1)]. The minimal metabolism in old age falls to 20 to 80 per cent. of the normal, while the daily exchange declines from the active period of life. An old man weighing 56 to 66 kilogrammes produces 1,400 to 1,800 calories —about 28 to 30 calories per kilogramme. The diminished amount of food taken has also to be considered. The amount of food which an old man needs is given in detail in Fenger's work. Old people are able to maintain nitrogenous equilibrium and also their body-weight upon an amount of food which yields 25 to 30 calories per kilogramme.

2. The Albumin Requirements.

The excretion of nitrogen by old workhouse inmates is very small. They eliminate about 5 to 12 grammes urea—5 to 8 grammes nitrogen daily. The investigations which accurate experiments in metabolic processes have entailed show that the aged need but little albumin; nevertheless, the figures obtained by Limbeck, Pfeiffer and Scholz and Kövesi (in one of his cases) are rather high when the light weight of his subjects is taken into consideration (1·5 to 2·0 grammes per kilogramme).[1] Rumpf gives 1·0 and 0·9 gramme per kilogramme in two cases; and Kövesi gives 0·7 gramme per kilogramme in one case (Nos. 3, 7, and 8*b* in the table) (2).[2]

In the last-mentioned cases, with a total food-supply of 38 to 26 calories, there was a small gain of nitrogen (0·1, 0·5, and 0·6 gramme daily). Similar results have been obtained in younger individuals. In the experiments of Sivèn, Lapicques [experiment (*a*)], Albus, and Chittenden [experiment (*a*)], the total amount of food given was arranged according to the weight of the subject, and did not exceed that given to the aged. In either case the result was made possible by a long-standing habit of small nitrogenous intake. In the table on p. 436 the relatively high nitrogen gain in Nos. 1, 2, 4, 5, 6, and 8 (*a*) was probably due to the fact that the albumin administered during the experiment exceeded the usual intake. Even if these experiments do not permit a definite statement that the amount of albumin required to maintain the aged in health is specially low, nevertheless they make it extremely probable. Attention should now be directed to the conditions which obtain when even smaller quantities than those taken in Chittenden's experiments are taken (2).

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[1] These figures are mostly obtained from workhouses in which, particularly in former days, animal food was but sparingly supplied.

[2] In Fenger's (2) case the supply of nitrogenous food was considerable. Nitrogen retention first appeared at 35 calories per kilogramme.

After a certain time, old people, of their own accord, begin to take less food than is required to keep up their weight. It is to this that the gradual loss of weight is due. Rumpf's two subjects—workhouse inmates—lost respectively 8 and 5½ kilogrammes in five and two years without any alteration in health. Each year does not necessarily bring about such a loss, and not every person over seventy to eighty years of age undergoes decrease in weight. Although certain results follow the sameness in diet, in institutions for the care of the aged poor the small amount of food is chiefly responsible for these losses in weight. Octogenarians of the upper classes are better preserved, and their appetite is stimulated by a well-varied diet, but even in such cases the intake will ultimately fall below the output. In old age the desire for food is no longer regulated by the amount requisite to maintain a metabolic equilibrium, as in earlier years. Even among the wealthy a gradual loss of weight takes place, although later, and to a less extent, than among the poor.[1] Although suitable diet and healthy conditions of life, to a great extent, make for longevity, they form only some of many influences which bear on the question.[2]

3. The Protein Decomposition.

So far as an opinion can be formed from the scanty data available, the degradation of albumin is unaltered in old age. Limbeck observed that in an aged woman the total output of nitrogen in the urine reached the highest normal limits—82·5 per cent. urea, the ammonia being 7·6 per cent. of the total nitrogen; while the average amount of uric acid—1·23 grammes—was fairly high. In two further cases Limbeck found the ammonia and uric acid to be normal, or below normal, the ammonia forming 3 to 5 per cent. of the total nitrogen excretion, the uric acid being 0·28 gramme (4). It is hardly possible that further observations would yield such wide discrepancies. Kronecker and Jakson found the nitrogenous output altered in old persons after the exer-

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[1] According to Quetelet (3) the average weight of man falls from 64 to 66 kilogrammes between the ages of twenty and fifty years, to 62 to 58 kilogrammes between fifty and seventy years; in women, from a maximum of 55 to 49 kilogrammes. The subjects of the table on p. 436 are almost all below this weight.

[2] Compare the interesting statements of Fenger (2).

EXPERIMENTS IN METABOLISM IN THE AGED.

No.	*Author.*	*Age and Sex.*	*Weight.*	*Food—* Calories. Total.	Calories. Per Kg.	Albumin. Total.	Albumin. Per Kg.	*Nitrogen.*	*Nitrogen Excreted.* Urine.	Fæces.	Total.	*Nitrogen Balance.*	*Increase in Weight.* Daily.	Total.	*Duration of Observations.*
			Kg.			Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Days.
1	Limbeck, I.	79 (f.)	37	1,290	34	71	1·9	11·4	9·46	0·57	10·0	+1·4	30	200	7
2	Limbeck, II. ..	81 (f.)	38	1,226	33	70	1·8	11·3	7·9	0·6	8·5	+2·9	70	400	6
3	Rumpf, I.	62 (f.)	42·2	1,606	38	43	1·0	6·9	5·6	1·2	6·8	+0·1	10	100	10[1]
4	Pfeiffer and Scholz, I.	81 (m.)	44·4	1,347	30·3	90	2·0	14·4	12·5	0·8	13·3	+1·1	20	100	4[2]
5	Pfeiffer and Scholz, II.	76 (f.)	45·3	1,347	29·7	90	2·0	14·4	12·3	0·7	13·0	+1·4	70	400	6[3]
6	Kövesi, I.	76 (f.)	45·0	1,128	25	66	1·5	10·6	8·1	0·7	8·8	+1·8	less	less	—
7	Rumpf, II.	68 (m.)	60·5	2,307	38	53	0·9	8·5	6·0	1·9	7·9	+0·6	0	0	12[4]
8	Kövesi, II. (*a*) ..	78 (f.)	61·0	1,220	20	66	1·1	10·6	7·0	0·4	7·4	+3·1	M. 25 days	—	9
	Kövesi, II. (*b*) ..	—	—	1,556	26	41	0·7	6·6	5·6	0·5	6·1	+0·5		130	9
	Kövesi, II. (*c*) ..	—	—	1,281	21	41	0·7	6·6	7·5	0·4	7·9	-1·4		9	9

[1] Very little exercise. [2] In bed. [3] In bed. [4] In a chair all day.

tions of mountaineering; but, on the other hand, the recent researches of A. Loewy show similar changes in young persons under similar circumstances (5). Probably this is merely a quantitative, not a qualitative alteration.

K. B. Hofmann and Grocco estimated 0·5 to 0·6 and 0·4 to 0·5 gramme creatinin in the urine of old persons, this being rather below the average found in adults (6). The excretion of creatinin depends, as does that of uric acid, on the amount of the mother-substances in the food from which it is derived.

Thus, the small amount of urine, low percentage of urea, solid residue, and salts which French authors have called the "characteristics of urine in the aged," and which they have analyzed with special care, is explained simply enough by the diminished food-supply required by the aged.

Albuminuria does not occur in healthy old people, even when their age is extreme [Demange, Th. Pfeiffer, N. Scholz, and others (7)], despite the fact that their kidneys almost invariably show definite atrophy.

4. Metabolism of Carbohydrates.

Primary glycosuria is rare [Maquard, Demange, Pfeiffer and Scholz (8)]. Even large doses of thyroid extract (6 to 12 tablets daily) do not cause it [Th. Pfeiffer and N. Scholz]. According to Aldor, an artificial glycosuria can be produced in 80 per cent. of cases by the administration of 130 to 150 grammes of grape-sugar. Possibly, however, the light weight (?) of the aged may explain the occurrence of glycosuria after the ingestion of such small quantities. The diminished activity of old kidneys is shown by the delayed appearance of glycosuria after the administration of phloridzin [Aldor (8)].

5. The Metabolism of Salts.

The urine of old persons contains the same amount of chlorides as that found in the young [Roche, Demange and Limbeck]. Von Bibra, on the other hand, found the amount to be greatly diminished (9). The determining point is the amount of chlorine contained in the food.[1]

The diminished sulphur excretion is explained by the diminished protein metabolism.

Neither sulphur nor chlorine belong to that class of elements whose quantities show much variation in health. The alkalis, about which we have been unable to find any statements,[2] do not appear to show any peculiarities.

The alkaline earths and phosphoric acid present points of greater interest. In old age the bones undergo atrophic changes similar to those occurring in the other organs. This atrophy shows itself as an increased porosity and a diminution in the contained lime and phosphates, such a diminution taking place very slowly. Even allowing that, during the period of greatest loss, an old man might lose one-fifth of his total bone salts—*i.e.*, about 280 grammes calcium and 200 grammes P_2O_5 (which is undoubtedly too high a figure)—the daily loss would only be 0·14 gramme calcium and 0·1 gramme phosphates. Pfeiffer and Scholz observed an excretion of 16·3 grammes P_2O_5 during six days in a man aged seventy-six, and 10·2 grammes in five days in a man seventy-eight years old. Their accompanying experiments with thyroid extract, however, gave 9·0 grammes in five and 7·8 grammes P_2O_5 in four days. There may, however, be periods of increased loss of phosphates compatible with metabolic equilibrium or even gain. The above-named authors attribute the excessive loss to the decrease in diet—the food contained only 2·09 to 2·27 grammes P_2O_5. According to Tigerstedt, 3 to 4 grammes P_2O_5 suffice for an adult man weighing 60 to 65 kilogrammes. According to this, the total excretion of 4 to 5 grammes P_2O_5 observed in persons weighing 45 kilogrammes is remarkably high, and cannot be satisfactorily explained by a small food-supply (10).[1] The proportions of the various phosphates in the urine and fæces of the above-mentioned cases was what would be expected from the food consumed (largely milk).

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[1] Fenger (2) found that with a diet almost confined to milk the sodium chloride was always under 2 per cent., often under 1 per cent.

[2] Von Bibra and Demange have published a few observations on the excretion of the urinary salts, but the food given in their cases was not stated.

Calcium.—A gradual loss is to be looked for here, as in the case of the phosphates. The amount that is accumulated in the degenerate tissues is quite negligible. There exist but few data concerning the intake and output of calcium in the aged. In order to avoid drawing false deductions, the power of the body slowly to accumulate calcium in considerable quantities must be remembered [Herxheimer]. When Rumpf (11) considers that this form of calcium retention has a bearing on arterio-sclerosis, it is impossible to agree to his conclusions, although we refrain from passing judgment on this suggestion of a calcium-free diet in the treatment of atheroma; only the merest traces of lime are deposited daily in sclerosed vessels, and the extent of calcification depends rather on the degenerate condition of the tissues than on the daily intake of calcium.

6. Water.

The daily excretion of water is perhaps slightly altered in old people; there is less evaporation from the colder and drier skin. Barral (12) makes this statement, and proves it by methods which are clear and satisfactory. Polyuria is not a characteristic of old age. This fact illustrates one of the differences between the kidney of old age and the contracted kidney, which anatomically somewhat resembles the normal senile kidney.

7. The Various Organs.

The absorption of food by the intestine is not lessened. The motions of old people are not exceptionally large or frequent. The percentages of loss by the stools are, as shown in the following table, about normal.

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[1] As a rule, when the urinary nitrogen output in old people is small, the amount of phosphates is only slight (*i.e.*, 0·66 gramme to 1·7 grammes P_2O_5).

ABSORPTION OF FOOD-STUFFS.

Percentage of Loss in Fæces.

Dried Residue.	*Nitrogen.*	*Fat.*	*Author* (13).
5·6–9·8	4·1– 5·1	6·2–10·0	Limbeck.
—	5·0– 6·0	—	Pfeiffer and Scholz.
—	2·0– 7·0	—	Kövesi.
—	17·0–22·0[1]	—	Rumpf.
—	5·5	5·0	Fenger.

Rumpf's higher figures are explained by the fact that his cases received an almost purely vegetarian diet. Menschoff found that the absorption of fats in old was quite as good as in young people (13).

Water Contents of the Muscular and Nervous Tissues.

It is generally accepted that senile muscular and nervous tissues contain but little water, being tough and dry. Against this there are a few observations of J. Ranke (14), according to which the organs of marasmic, but not dropsical, old persons contain more water than those of young adults.

WATER CONTENTS OF THE ORGANS.

	Muscles.	*Total Cerebral Tissues.*	*Cerebral Tissue—* White.	*Cerebral Tissue—* Grey.	*Spinal Cord.*	*Author* (14).
Man aged sixty-four years	84·8	80·5	73·0	87·2	72·9	J. Ranke.
Woman aged seventy-three years ..	81·2	77·2	67·8	83·6	70·8	J. Ranke.
Man and woman aged seventy and ninety-four years	—	—	72·2–72·6	84·0–84·8	—	Weisbach.
Younger persons ..	—	—	63·8–70·3	82·6–83·6	—	Weisbach.
Younger persons ..	About 75–79	78–79	70–73	83–85	69·7	Various.

Von Bibra also gives a higher estimate of the water contents of nervous tissues. Their relative increase may be brought about by the diminution of substances soluble in ether.

Further researches on the water in muscles and parenchymatous organs are required. An increase in dry constituents is seen in the atheromatous aorta (Gazert), but this depends chiefly on the calcification of the degenerated areas.

It has long been pointed out that the blood of old persons contains a diminished number of cells. Quinquaud (15) found an average of 3,640,000 red blood-corpuscles in old people of eighty-seven years;

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[1] Vegetarian diet, with much vegetables.

Duperié and Sörensen found from 4,200,000 to 4,700,000 in old persons over seventy years. Quinquaud estimated the hæmoglobin at about 60 per cent. Masjoutin, however, found it unaltered in thirteen cases.

Limbeck estimated the alkalinity of the serum at 0·205 to 0·29 gramme NaOH per 100 c.c. This shows little variation from the estimation he obtained by the same methods in the case of younger people (0·25 to 0·28 gramme NaOH).

The amount of cholesterin present is also increased—according to trustworthy authors [Bequerel and Rodier, v. Bibra (16)]—to 0·29 to 0·32 gramme per 100 c.c. blood.

The proportion of urea in the blood of old persons may be high—0·032—compared with the normal of 0·017 to 0·019 [Quinquaud (17)]; this, perhaps, arises from the slower eliminating power of the kidneys.

In old age the mineral constituents of the bones (diaphyses) diminish somewhat (62 to 65 per cent.), while the organic components are slightly increased [Sappey and Nélaton (18)]. This fact is explained by the partial replacement of true bone tissue by enlarged bloodvessels and bone-marrow.

The appearance of old age, with its accompanying loss of vigour, is ascribed by different authors to the atrophy of one or other organ or system. One considers it to be due to the involution of the organs of generation, another to atrophy of the intestine, which prevents the absorption and assimilation of a sufficient quantity of food. Demange considers the cause of old age to be a primary change in the arterial system, which in its turn leads to inadequate nutrition of the body generally. Horsley and H. Lorand ascribe the senile appearances to the atrophy of the thyroid gland. To an impartial mind none of these explanations is sufficient. Even if the atrophy of different organs is of varying portent according to their physiological importance, it does not appear likely that the primary decay of one group of cells should of necessity result in the atrophy of all. The old age of the whole body consists of a "wearing out," which is common to all the physiologically important cells. Metchnikoff expresses it in the following manner: "Old age is characterized by a conflict between the finer and more complicated elements and the simple or more primitive elements of the organism—a conflict that ends to the advantage of the latter. The picture is always the same—atrophy of the more highly differentiated elements and their replacement by an overgrowth of connective tissue" (19). It is true that one organ may exhibit degenerative changes before the rest—the involution of the ovary affords the best example of this kind—but it does not thereby involve the degeneration of the whole body. The conditions which follow castration differ strikingly from those of old age. The premature atrophy of the thyroid gland is not followed by old age, but by a peculiar form of cachexia.[1]

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[1] The "comparisons" collected by Lorand are, however, merely superficial. In the one case, as in the other, many changes take place in appearance and in vigour; but, as a matter of fact, there are vast differences. In order to carry the comparison between old age and myxœdema to its logical conclusion, a comparison must also be drawn between youth and exophthalmic goître.

The border-line which divides physiology from pathology is crossed in any case in which the degeneration of any vital organ precedes that of the rest of the body. When Demange ascribed old age to arterial degeneration, he did so with good reason, as, unlike other observers, he never failed to obtain evidence of it in his healthy workhouse patients. The hypothesis receives the strongest support from the fact that very considerable arterial change is often present, and remains unsuspected for many years. The hypertrophy of the heart, the one organ which almost invariably is found to be enlarged in old age, can compensate for a long time for premature and excessive arterial degeneration.

If Demange is under the impression that arterio-sclerosis is a pathological condition, surely, according to him, old age must also be pathological; as the degeneration increases, death must be the conclusion of an illness, and not the natural extinction of life. The high average duration of life among the Heligoland boatmen is well known, and 75 per cent. of their deaths are due to cerebral hæmorrhage.

The kidneys of old people show a gradual loss of renal epithelium and in this they simulate small contracted kidneys; but the essential features of chronic interstitial nephritis are absent, the functions being normally performed. Should the kidneys, however, degenerate with undue rapidity, the clinical picture of contracted kidney is produced. In such a case as that of three brothers in whose history no known cause of renal cirrhosis was found, yet who all developed that malady between sixty and seventy years of age, one cannot ascribe the cause to premature senility.[1]

Physiological old age can only be said to exist when the involution of the various organs takes place gradually and at the same rate. Metchnikoff's Biblical quotation applies to such cases: "And his days were ended and he died, for he was old and weary of his life." In such rare cases of simple old age death may occur quietly, like a deep sleep; and at the autopsy those changes which commonly cause the sudden extinction of the "light of life" are seldom present.

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[1] Are not numerous diseases of adult life which result in chronic atrophy (*i.e.*, in the invasion of important tissues by connective tissue) to be ascribed to premature old age? No other explanation seems to hold good in the matter of renal deficiencies, which result in the death of many members of one family from interstitial nephritis [Pel and others]. What else will explain the fact that the same type of attack which may be borne without ill-effect by healthy old persons aged eighty to ninety years, will in other cases result in throwing the kidneys prematurely out of gear? Is it not possible similarly to interpret many cases of hepatic cirrhosis and myxœdema which have arisen without any apparent cause, such as chemical or toxæmic poisoning? The body and all its organs are slowly and gradually worn out as life proceeds. If any one organ wears out prematurely without any undue strain, "hereditary weakness" may be considered as being a predisposing cause of premature old age.

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